Physical and Mental Activity, Disease Susceptibility, and Risk of Dementia: A Prospective Cohort Study Based on UK Biobank

Author(s):
Jianwei Zhu, MD, PhD1; Fenfen Ge, PhD2,3; Yu Zeng, MD2,3; Yuanyuan Qu, MA2,3; Wenwen Chen, MD4; Huazhen Yang, MD2,3; Lei Yang, PhD5; Fang Fang, MD, PhD6; Huan Song, MD, PhD2,3,7

Corresponding Author:
Huan Song, songhuan@wchscu.cn

Affiliation Information for All Authors: 1. Department of Orthopedic Surgery and National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University, Chengdu 610041, China; 2. West China Biomedical Big Data Center, West China Hospital, Sichuan University, Chengdu, China; 3. Medical Big Data Center, Sichuan University, Chengdu, China; 4. Division of Nephrology, Kidney Research Institute, State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University, Chengdu, China; 5. Department of Anesthesiology, West China Hospital, Sichuan University, Chengdu, China; 6. Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden; 7. Center of Public Health Sciences, Faculty of Medicine, University of Iceland, Reykjavik, Iceland

Neurology® Published Ahead of Print articles have been peer reviewed and accepted for publication. This manuscript will be published in its final form after copyediting, page composition, and review of proofs. Errors that could affect the content may be corrected during these processes.

Copyright © 2022 American Academy of Neurology. Unauthorized reproduction of this article is prohibited
Equal Author Contribution:
Jianwei Zhu and Fenfen Ge contributed equally to the study.

Contributions:
Jianwei Zhu: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data
Fenfen Ge: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Yu Zeng: Analysis or interpretation of data
Yuanyuan Qu: Major role in the acquisition of data
Wenwen Chen: Major role in the acquisition of data; Analysis or interpretation of data
Huazhen Yang: Major role in the acquisition of data
Lei Yang: Analysis or interpretation of data
Fang Fang: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Huan Song: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data

Figure Count:
6

Table Count:
1

Search Terms:
[25] All Cognitive Disorders/Dementia, [26] Alzheimer's disease, [54] Cohort studies, [95] Association studies in genetics

Acknowledgment:
This research was done using the UK Biobank Resource under Application 54803. We thank the team members and colleagues involved in West China Biomedical Big Data Center- UK Biobank project for their support.

Study Funding:
This work was supported by the National Natural Science Foundation of China (No. 81971262 to HS), 1.3.5 project for disciplines of excellence, West China Hospital, Sichuan University (No. ZYYC21005 to HS and No. ZYGD20005 to LY), and National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University (No. Z20201013 to HS).

Disclosures:
Copyright © 2022 American Academy of Neurology. Unauthorized reproduction of this article is prohibited
ABSTRACT

Background and objectives: The association between patterns of physical/mental activity and dementia and how it is affected by disease susceptibility remains unknown. We aimed to examine the association between patterns of physical and mental activity and dementia, and whether it can be modified by disease susceptibility to dementia.

Methods: In a prospective cohort study based on UK Biobank, 501,376 dementia-free participants were recruited in 2006-2010 and followed from one year after the recruitment date until the end of 2019 for ascertainment of dementia. Data on physical (i.e., physical activity at leisure time, housework-related activity, and transportation) and mental (i.e., intelligence, social contact, and use of electronic device) activity were collected using questionnaires at recruitment. Cox models were used to estimate the associations of physical and mental activity-related items, as well as major activity patterns identified by principal component analysis, with the risk of dementia, adjusted for multiple confounders. The modification role of disease susceptibility on such associations was assessed through stratified analyses by polygenic risk score.
(PRS) of dementia generated based on summary statistics of independent genome-wide association studies, by apolipoprotein E (APOE) genotype, and by self-reported family history of dementia.

**Results:** The mean age at recruitment was 56.53, and 45.60% of the participants were male. During a mean follow-up of 10.66 years, 5,185 dementia cases were identified. When analyzed separately, multiple studied items related to physical and mental activity showed significant associations with the risk of dementia. The pattern analyses revealed that higher level of adherence to activity patterns related to frequent vigorous and other exercises (hazard ratio [HR]=0.65, 95% confidence interval [CI] 0.59-0.71), housework-related activity (0.79, 0.72-0.85) and friend/family visit (0.85, 0.75-0.96) were associated with a lower risk of dementia. We obtained comparable results for vascular dementia and Alzheimer’s disease as well as in the stratified analyses by PRS for dementia, APOE genotype, or family history of dementia.

**Conclusion:** Activity patterns more adherent to frequent vigorous and other exercises, housework-related activity, and friend/family visit were associated with a reduced risk of multiple types of dementia. Such associations are independent of disease susceptibility, highlighting the potential of these physical and mental activity patterns, as effective interventions, in the primary prevention of dementia.

**Keywords:** dementia, physical activity, mental activity, principal component analysis, polygenic risk score
INTRODUCTION

Dementia is one of the leading causes for dependence and disability among the elderly, affecting approximately 50 million people worldwide with nearly 10 million newly diagnosed cases per year\(^1\). Previous studies have identified several potential risk factors, including educational level, smoking, obesity, alcohol drinking, hypertension, hearing impairment, depression, and diabetes for dementia\(^2\). Significant gaps remain however regarding the knowledge about modifiable risk factors and their potential role in the prevention of dementia.

A growing body of evidence supports the role of physical activity in maintaining cognitive capacity and preventing dementia\(^3,4\). Meta-analyses of observational studies consistently indicated an association between exercise and reduced risk of dementia\(^5\), especially Alzheimer’s disease\(^6\). However, due to the heterogeneity of physical activity measurements and methodologies (including sample size) of previous studies, knowledge about effective physical activity mode and intensity, in terms of dementia prevention, remains limited. One further concern is that multiple modes of physical activity are correlated and might interact with each other (i.e., persons who are physically active tend to have high levels of many types of physical activities). It is therefore necessary to consider such correlations and study overall patterns of physical activity. Similar attempts are also needed to elucidate the role of mental activity, such as visiting friends and playing computer games, on the risk of dementia, for which suggestive evidence has been provided in a few previous studies on
Disease susceptibility plays an important role in the development of dementia\textsuperscript{10, 11}. For instance, the epsilon4 (\(\varepsilon_4\)) allele of apolipoprotein E (APOE) gene has been identified as the most well-established genetic risk factor for late-onset Alzheimer’s disease\textsuperscript{12}. In addition, numerous genome-wide association studies (GWAS) have recently uncovered more genetic variants associated with the risk of dementia\textsuperscript{13, 14}, with an estimated disease heritability ranging from 13\% to 80\%\textsuperscript{15}. Thus, explorations on potential modifiable risk factors for dementia need to take into consideration an individual’s inherent genetic susceptibility, with the aim to achieve better precision prevention.

In the present study, based on enriched phenotype information from the community-based UK Biobank cohort, together with individual-level genotype data and complete follow-up data on medical diagnoses, we aimed to assess the associations between physical and mental activity and the subsequent risk of dementia. We further explored whether such associations would differ for individuals with different susceptibility to dementia.

**METHODS**

**Data source and study design**

UK Biobank is an ongoing prospective cohort study which recruited over 500,000 participants aged 40-69 years during 2006-2010 from England, Scotland and Wales\textsuperscript{16}. 

Copyright © 2022 American Academy of Neurology. Unauthorized reproduction of this article is prohibited
Information about sociodemographic characteristics, lifestyle factors (e.g., physical and mental activity), and medical and health conditions, as well as physical measures (e.g., anthropometry), was collected from all participants at recruitment. Data on medical diagnoses and survival status were derived by cross-linkage with multiple national health registers, including primary care, hospital inpatient, cancer, and death registers.

In the present study, among all 502,507 individuals in the UK Biobank, we excluded participants who withdrew their data (n=48), were diagnosed with dementia before recruitment (n=120), or had no available information on physical and mental activity (n=963) (Figure 1). Separate cohorts were constructed to analyze 30 different items of physical and mental activity measured at baseline, where participants with missing value for a specific item were removed from the analysis of this specific item. The remaining participants were then assigned into different groups according to their corresponding exposure levels (i.e., reference and exposed groups). Taking into consideration the potential diagnostic delay of dementia and thereby the risk of reverse causality (i.e., the self-reported physical and mental activities were influenced by preclinical symptoms of dementia), we started the follow-up for each participant from one year after the recruitment date (i.e., 1-year lag-time) until a diagnosis of dementia, death, or the end of study (i.e., 31 December 2019), whichever occurred first. The final analytic cohort included 501,376 participants.

**Standard protocol approvals, registrations, and patients**
consents

All UK Biobank participants signed informed consent before information collection and the study has full ethical approval from the NHS National Research Ethics Service (16/NW/0274). The present study (study protocol can be found in the supplement) was also approved by the biomedical research ethics committee of West China Hospital (reference number: 2019-1171).

Measurements of physical and mental activity

Physical activity was assessed by 21 items from the well-validated short self-reported International Physical Activity Questionnaire (IPAQ) at recruitment. There were five major categories, including physical activity at leisure time (i.e., strenuous sports, other exercise, walking for pleasure, and climbing a flight of stairs), housework-related activity (e.g., heavy DIY and light DIY), job-related activity (i.e., job involved standing or walking and job involved heavy manual or physical activity), transportation for work (i.e., by walk, cycle, car and public transport), and transportation for others (i.e., by walk, cycle, car and public transport). For specific physical activity within the first two categories, participants reported their attendance (yes or no), frequency (days/week) and duration (minutes/day). Additional information is available in eTable 1 in the Supplement.

We considered mental activity as conditions related to intelligence, social contact and electronic device use, adherent to definitions used in previous studies.
Specifically, in this study, items related to intelligence (i.e., educational level and attendance of adult education classes), social contact (i.e., attendance and frequency of friend/family visit, pub or social club visit, religious and other group activity), and use of electronic device (i.e., frequency of playing computer games, watching TV, and making or receiving calls on a mobile phone) were extracted from touchscreen questionnaires collected at baseline (eTable 1).

**Ascertainment of dementia**

We identified cases of dementia from the UK Biobank inpatient data, according to corresponding codes of International Classification of Diseases (ICD) coding system (eTable 2). We also analyzed subtypes of dementia, including vascular dementia, Alzheimer’s disease and other dementia (eTable 2). Diagnosis of dementia from UK Biobank inpatient data has previously been validated, showing a positive predictive value of 87.3% and 68.2% for any dementia and Alzheimer’s disease, respectively, compared with clinical expert adjudication of full-text medical records21.

**Disease susceptibility to dementia**

We assessed the disease susceptibility to dementia by polygenic risk score (PRS) for dementia, APOE genotype, and family history of dementia. PRS, representing an individual’s load of common genetic variants to a specific trait, was estimated based on GWAS summary statistics of Alzheimer's disease from independent populations22. Specifically, based on the UK Biobank imputed genotype data, our analysis was
restricted to the autosomal biallelic SNPs. Variants with a call rate <98%, a minor allele frequency <0.01, or deviation from Hardy-Weinberg equilibrium (P<10^{-6}) were removed from the analysis. We further excluded individuals with genotyping rate <98%, outlier samples based on abnormal heterozygosity level, and up to the second related individuals (kinship coefficient≥0.0884). The final analysis included 6,099,107 SNPs for 376,869 participants. We computed PRSs under ten p value thresholds (i.e., 5 × 10^{-8}, 1 × 10^{-6}, 1 × 10^{-4}, 1 × 10^{-3}, 0.05, 0.1, 0.2, 0.3, 0.4 and 0.5), using the weighted method described previously\(^{22}\). In a validated step, the PRS with the highest Nagelkerke’s squared (corresponding to a p threshold of 5 × 10^{-8} with 13 included SNPs) was selected for further analysis, which showed an association with risk of dementia in our dataset (odds ratio=1.21, 95% confidence interval [CI] 1.17-1.25 per one unit increase in PRS).

Further, as the ε4 allele of APOE gene has been established as a genetic risk factor for late-onset Alzheimer’s disease, we determined the APOE genotype by APOE SNPs rs429358 and rs7412, where participants with 1 or 2 ε4 alleles were considered as APOE ε4 carriers and the others as APOE ε4 noncarriers\(^{23}\). In addition, family history of dementia was defined as dementia among any first-degree relative (father, mother and siblings) according to the self-report information at baseline. It was regarded as an index of joint effect of genetic background and early-upbringing environmental and lifestyle factors.

Covariates
Data on demographic factors (sex, age, and race and ethnicity), socioeconomic factors (income and education), lifestyle (alcohol drinking and smoking status) were collected at baseline through questionnaires. Body mass index (BMI) was constructed from height and weight measured at the initial assessment center visit. Townsend deprivation index (TDI) was calculated based on the postcode of family address, representing levels of area-based deprivation\textsuperscript{24}. Charlson comorbidity index (CCI) was calculated, as a proxy of baseline somatic fitness, summarizing the presence of 18 medical conditions (see details in the \textit{eTable 2})\textsuperscript{25} based on UK Biobank inpatient data. As individuals with prevalent dementia were excluded from the analysis, the CCI calculation did not include dementia. In addition, we obtained information about history of hypertension and hyperlipidemia based on medical diagnoses from primary care and inpatient hospital data (\textit{eTable 2}). Cognitive function was evaluated by validated fully-automated UK Biobank cognitive tests\textsuperscript{26} at recruitment. We used reaction time as an indicator of baseline cognitive function, with higher score associated with poorer overall performance.

\textbf{Statistical analysis}

\textit{Identification of patterns of physical and mental activity}

We identified patterns of physical and mental activity, using principal component analysis (PCA). Briefly, PCA provides low-dimensional information extracted from numbers of variables with high correlations, which thereby enables the identification
of distinct behavior patterns of major relevance, presented as significant principal components (PCs). The analysis was performed among 407,735 participants for physical activity, and 231,141 participants for mental activity, as individuals with any missing values were removed (Figure 1). We retained PCs with the highest eigenvalues and cumulatively explained variance over 50%. The PC score was calculated through integrating all included variables weighted by their factor loadings in this PC, with higher PC scores indicating greater adherence to the specific pattern. In the pattern analyses for each PC, the PC scores of all participants were ordered from the lowest to the highest, and categorized into low, moderate, and high groups according to tertile distribution (low:< 1st tertile, moderate: 1st-2nd tertile, and high: >2nd tertile).

**Phenotypic associations of physical and mental activity with subsequent dementia**

We assessed the associations between individual items of physical and mental activity, as well as patterns of physical and mental activity, and dementia using Cox regression models, represented as hazard ratios (HRs) and their 95% CIs. We first performed analysis for any dementia, and then for vascular dementia, Alzheimer’s disease, and other dementia. In all models, we adjusted for age (as continuous variable), sex (male or female), race and ethnicity (White, Asian, Black, Mixed, or unknown), TDI (as continuous variable), education (college/university degree: yes, no, or unknown), income (<£18,000, £18,000-£30,999, £31,000-£51,999, £52,000-£74,999, £75,000-£104,999, £105,000-£149,999, £150,000-£199,999, £200,000-£299,999, £300,000-£499,999, £500,000-£999,999, £1,000,000 or more), and any other factors that might influence the outcomes.
£52,000-£100,000, >£100,000, or unknown), smoking and alcohol status (never, previous, current, or unknown), BMI (<18.5, 18.5-24.9, 25.0-29.9, ≥30.0 kg/m², or unknown), CCI (0 or ≥1), history of hypertension (yes or no), history of hyperlipidemia (yes or no), and family history of dementia (yes, no, or unknown).

We also performed subgroup analysis by age group (≤65 years or >65 years), sex (male or female) and income level (<£18,000, £18,000-£51,999, or ≥£52,000).

The modification role of disease susceptibility to dementia on the phenotypic associations

To explore whether the associations between patterns of physical and mental activity and dementia might be modified by disease susceptibility, we performed stratified analyses by PRS for dementia (high: >2nd tertile or low: <1st tertile), APOE genotype (APOE ε4 carrier or noncarrier), and family history of dementia (with or without).

Given that dementia patients who received ‘other dementia’ as the initial clinical diagnosis were likely to be re-classified as other subtypes of dementia later, we re-assessed the HRs for subtypes of dementia by allowing such a change in diagnosis during follow-up. Further, using a sample of 496,667 participants with available results of reaction time from cognitive tests, we conducted sensitivity analyses by either additionally adjusting for or stratifying the analysis by different cognitive performance levels at baseline (i.e., using tertiles of reaction time: high < 1st tertile, moderate 1st-2nd tertile, or low >2nd tertile), considering that cognitive decline may be
a prodromal phase of dementia\textsuperscript{28}. To deal with the possible correlation between patterns of physical and mental activity, we repeated the pattern analyses of physical activity by additionally adjusting for all meaningful PCs of mental activity, and \textit{vice versa}, among participants with data on all physical and mental activity-related items at baseline (n=199,045). In addition, to further test the robustness of our results to the concern of reverse causality\textsuperscript{18}, we applied 5-year and 10-year lag time (i.e., started the follow-up 5 or 10 years after the recruitment date), instead of 1-year lag time as used in the main analysis.

All data analyses were completed using R-4.0 software and Plink-1.9. A 2-tailed test with P < 0.05 was considered statistically significant.

Data availability

Data from the UK Biobank (http://www.ukbiobank.ac.uk/) are available to all researchers upon making an application.

RESULTS

The mean age at recruitment was 56.53, and 45.60\% (228,555/501,376) of the participants were male. During a mean follow-up of 10.66 years, 5,185 cases of dementia were identified, including 803 cases of vascular dementia, 1,561 cases of Alzheimer's disease, and 2,697 cases of other dementia. Table 1 shows characteristics of participants with any or specific subtypes of dementia, and those without dementia. Compared to other participants, the participants who developed dementia during
follow-up were more likely to be older, male, have a history of hypertension or hyperlipidemia, and with lower socioeconomic status but higher BMI and CCI at baseline. Few differences regarding the characteristics were noted between individuals who developed different subtypes of dementia.

**Associations between items related to physical/mental activity and subsequent dementia**

For physical activity, a higher level of the most studied items was associated with a lower risk for dementia, with the strongest (represented by deeper degree of green color) association observed for items related to job-related activity and transportation (Figure 2 and eTable 3). For mental activity, while visiting pub or social club (HR=1.07, 95%CI 0.99-1.15) and watching TV (HR=1.07, 95%CI 1.05-1.09) seemed to be associated with a higher risk of dementia, the attendance of friend/family visit (HR=0.66, 95%CI 0.56-0.77) and other group activity (HR=0.91, 95%CI 0.85-0.98) was associated with a lower risk of dementia (Figure 2 and eTable 4). The result pattern was largely similar for different subtypes of dementia (eTable 3 and 4).

**Associations of identified physical or mental activity patterns with subsequent dementia**

In the PCA, five PCs, accounting for 50.2% of the total variance, were identified for physical activity (see eFigure 1 in the supplement). We labeled each pattern by its contributing factors with top loading values, which was then named as pattern most
related to ‘vigorous and other exercise at leisure time’, ‘housework-related activity’, ‘transport-related activity’, ‘job-related activity’, and ‘walking for pleasure’, respectively. Similarly, we recognized four PCs for mental activity (accounting for 52.5% of the total variance), named as patterns most related to ‘pub or social club visit’, ‘watching TV’, ‘attending other group activity/adult education classes’, and ‘friend/family visit’ (eFigure 2).

**Figures 3 and 4** show the HRs and 95% CIs for any and different subtypes of dementia by different levels of adherence to each physical/mental activity pattern, using the low PC score group as the reference. For physical activity, we observed a lower risk of dementia in relation to a greater adherence to patterns related to frequent vigorous and other exercise (high vs low, HR=0.65, 95% CI 0.59-0.71) and housework-related activity (high vs low, HR=0.79, 95% CI 0.72-0.85), whilst null results were found for other identified patterns. Similar findings were noted for all subtypes of dementia. For mental activity, we observed a lower risk of dementia in relation to a greater adherence to the pattern of friend/family visit, with a HR of 0.85 (95% CI 0.75-0.96) when comparing individuals with high vs low PC score. In the analysis of subtypes, a statistically significant association was only noted for other dementia (high vs low, HR=0.85, 95% CI 0.71-1.00).

We obtained similar results across different groups of age at recruitment (eTable 5), sex (eTable 6), and income level (eTable 7).

**The modification role of disease susceptibility to dementia on the**
**observed associations**

The associations were largely comparable for individuals with high and low genetic risk of dementia, measured by PRS (Figure 5) or APOE genotype (eTable 8). For instance, the HR was 0.64 (95% CI 0.52-0.77) and 0.68 (95% CI 0.57-0.79) for a greater adherence to vigorous and other exercises pattern among individuals with low and high genetic risk for dementia, respectively. The corresponding HRs were 0.63 (95% CI 0.54-0.72) and 0.68 (95% CI 0.59-0.78) among APOE ε4 carriers and noncarriers, respectively. Similar results were also noted among participants with and without a family history of dementia (e.g., for vigorous and other exercise pattern, HR=0.64 [95% CI 0.52-0.79] for individuals with family history of dementia and HR=0.69 [95% CI 0.60-0.78] for individuals without, Figure 6).

In sensitivity analyses, the observed estimates for subtypes of dementia remained identical after allowing a change in the initial ‘other dementia’ diagnosis (28.7% [763/2660] of other dementia cases experienced a changed diagnosis, see eTable 9). Further adjustment for or stratification by level of cognitive function at baseline did not change the results greatly (eTable 10 and 11). Likewise, re-assessing the HRs for PCs of physical activity by additionally adjusting for significant PCs of mental activity, and *vice versa*, led to largely similar results (eTable 12). We further obtained similar point estimates when 5- or 10-year lag time was used in the analyses of physical activity patterns. However, with reduced number of cases in these new lag-time analyses, no statistically significant association was noted in the analysis of
ment activity patterns (eTable 13).

**DISCUSSION**

Based on a large cohort of 501,376 UK Biobank participants, our study indicated that both physical and mental activity could influence the risk of dementia among the elderly. Particularly, we used PCA to identify distinct patterns of physical and mental activity based on correlated individual activity items, and found that individuals with a greater adherence to activity patterns related to frequent vigorous and other exercise at leisure time, housework-related activity, and friend/family visit had a reduced risk of multiple types of dementia. Furthermore, our findings based on the stratified analysis by PRS for dementia, APOE genotype, and family history of dementia consistently revealed that the protective role of these physical and mental activity patterns was present for all study participants, irrespective of different disease susceptibilities. This novel finding highlights the potential of physical and mental activity interventions in the primary prevention of dementia for the general population.

Our finding of a decreased risk of dementia among individuals with a higher level of physical activity is consistent with previous studies. For instance, individuals with the highest level of physical activity were noticed to have a 28% decreased risk for dementia (45% for Alzheimer's disease), compared to those with the lowest level, in a meta-analysis of 163,797 individuals from 16 studies. Similarly, another meta-analysis of 15 prospective studies involving 33,816 individuals concluded that
physical activity could protect nondemented individuals against cognitive decline during a follow-up of 1-12 years. However, null findings have also been reported. A few randomized controlled trials (RCTs) failed to indicate cognitive benefit from aerobic exercise for cognitively healthy participants. Besides the heterogeneity in the measurement or definition of physical activity exposures (e.g., type, frequency, and duration), the limited sample size and follow-up period, particularly in RCTs, and the incomplete consideration of other important factors, such as other lifestyle factors and disease susceptibility, might have contributed to the inconsistent results. Moreover, every individual has multiple types of physical activity in their daily life which closely correlate and interact. Although attempts have been made to explore the most beneficial types of physical activity, limited attention has been given to the interactions between physical activity-related factors. In the present study, we applied the cluster analysis to identify patterns of physical activity, instead of using individual items separately, for the association analyses. Indeed, despite of significant results observed for most studied items of physical activity, only vigorous and other exercise at leisure time and housework-related activity were associated with a reduced risk of dementia, after considering overall physical activity pattern (i.e., the exposure level of other physical activities of the same individual). In addition, it is worthwhile to note that although physical activity might be a possible preventive measure in the pre-dementia stage, the role of vigorous activity among clinically diagnosed dementia patients remains less clear. For example, a recent multicenter randomized clinical trial of 494 patients with dementia indicated potentially greater cognitive impairment
among dementia patients who received a 12-month aerobic and strength exercise program, compared with the controls, although the difference between the intervention and control groups was relatively small and not statistically significant\textsuperscript{35}. Similar phenomenon was noted in the analysis of mental activity. While multiple mental activity-related factors showed negative associations with dementia when analyzed separately (e.g., high educational attainment as noted in previous reports\textsuperscript{36}), only the pattern featured by frequent friend/family visit was linked to reduced risk of dementia in the analysis of mental activity pattern. Together with our novel finding that the protective effect of these physical and mental activity patterns did not differ by disease susceptibility to dementia, these results highlight the importance of leisure time physical exercise, housework-related activity, and active social contact in the prevention of dementia for elderly population.

The underlying mechanisms linking physical activity with a decreased risk of dementia remain unknown. Several possible explanations have been proposed, including the neuroprotective effect of physical exercise possibly through promoting release of brain-derived neurotrophic factors\textsuperscript{37,38}. Also, regular aerobic exercise may improve cerebral blood flow and thus reduce the development of age-associated decline\textsuperscript{39}. In addition, exercise has been proven to have antioxidant effects\textsuperscript{40} and may consequently delay the oxidative damage in brain, which is the hallmark of dementia pathogenesis\textsuperscript{41}. Further, physical activity can indirectly influence other modifiable factors for cognitive function, including obesity, hypertension, insulin resistance,
depression, and cardiovascular fitness\textsuperscript{42,43}. Finally, our results of mental activity pattern reinforce the benefit of social contact (e.g., friend/family visit), as social isolation might directly result in cognitive inactivity or faster cognitive decline\textsuperscript{44}, and indirectly influence functions of brain though increasing the risk of cardiovascular disease\textsuperscript{45} and depression\textsuperscript{46}.

The major merit of our study is the use of the UK Biobank data, a database with a community-based cohort design, detailed data on physical and mental activity and other lifestyle factors, and a complete follow-up of more than 10 years. The large sample size enables the performance of important subgroup analyses. For instance, although the study cohort was relatively young, the age-specific analysis showed similar results between individuals at 65 or younger and those above 65 at baseline, suggesting that the associations noted in the present study are likely applicable to both early- and late-onset dementia. The collection of physical and mental activity data and dementia was conducted independently, minimizing the risk of differential information bias. In addition, besides a screening on the associations for all relevant items of physical and mental activity, we used PCA to detect the specific patterns of physical and mental activity in the study population which allowed the consideration of multiple activity-related items simultaneously. Moreover, we were able to consider the disease susceptibility to dementia by level of PRS or APOE genotype (based on individual-level genotype data) and family history of dementia (self-reported) which demonstrated a universal importance of physical and mental activity patterns on dementia among individuals with different disease susceptibility. Last, with the
availability of enriched information from the comprehensive questionnaire surveys, we were able to control for a wide range of important factors, including different cognitive performance level at baseline.

Notable limitations include the measurement of physical and mental activity based on self-reported questionnaire at recruitment, leading to the concern of information bias due to recall or lack of repeated measurements. Further studies, with objective and repeated surveillance on physical and mental activity, are warranted. Second, as diagnostic delay is common for dementia, the observed associations were subject to reverse causality, although we applied 1-year lag time in the main analyses. However, such concern should have been partially released by the similar results obtained in the sensitivity analyses using 5- or 10-year lag time. Further, the accuracy of dementia subtype diagnosis is likely unsatisfactory, which might have led to a concern of misclassification between subtypes of dementia, particularly between vascular and other dementias. In our data, we found that approximately 30% of other dementia cases received a diagnosis of another dementia subtype during follow-up. This does however not seem to influence our results. Anyway, future studies with accurate classification of dementia subtypes are still warranted. Last, the UK Biobank participants are not representative of the general UK population, given that its baseline survey has a low response rate (6% of the invited individuals participated in the study)\textsuperscript{47, 48}. However, despite of such a bias, the reproducibility of findings from UK Biobank-based risk factor studies, such as those focusing on cardiovascular disease and cancer outcomes, has been shown as satisfactory\textsuperscript{49}. Regardless, the
generalizability of our findings to the whole UK or other populations needs to be tested.

In conclusion, based on the longitudinal cohort of UK Biobank, a greater adherence to a physical activity pattern of frequent vigorous and other exercise or housework-related activity, and a greater adherence to a mental activity pattern of friend/family visit, are associated with a lower risk of multiple types of dementia. Moreover, as the suggested protective effects of these activity patterns were consistently observed among individuals with different disease susceptibilities, such findings further underscore the potential of these identified physical and mental activity patterns, as effective interventive strategies, for the primary prevention of dementia among the general population.

Contributions

JW and HS has full access to the data used in the analyses in the manuscript. HS, FF, and JW were responsible for the study concept and design. FG, YZ, YQ, HY, and YH, did the data and project management. FG, YZ, and WC did the data cleaning and analysis. HS, JW, FG, and FF interpreted the data. JW, FG, FF, and HS drafted the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been
omitted.
References

1. Larson EB, Yaffe K, Langa KM. New insights into the dementia epidemic. The New England journal of medicine 2013;369:2275-2277.
2. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet 2020;396:413-446.
3. Angevaren M, Aufdemkampe G, Verhaar HJ, Aleman A, Vanhees L. Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. The Cochrane database of systematic reviews 2008;Cd005381.
4. Walsh EL, Smith L, Northey J, Rattray B, Cherbuin N. Towards an understanding of the physical activity-BDNF-cognition triumvirate: A review of associations and dosage. Ageing research reviews 2020;60:101044.
5. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. Lancet 2017;390:2673-2734.
6. Hersi M, Irvine B, Gupta P, Gomes J, Birkett N, Krewski D. Risk factors associated with the onset and progression of Alzheimer's disease: A systematic review of the evidence. Neurotoxicology 2017;61:143-187.
7. West GL, Zendel BR, Konishi K, et al. Playing Super Mario 64 increases hippocampal grey matter in older adults. PLOS ONE 2017;12:e0187779.
8. Sommerlad A, Sabia S, Singh-Manoux A, Lewis G, Livingston G. Association of social contact with dementia and cognition: 28-year follow-up of the Whitehall II cohort study. PLoS medicine 2019;16:e1002862.
9. Chan D, Shafto M, Kievit R, et al. Lifestyle activities in mid-life contribute to cognitive reserve in late-life, independent of education, occupation, and late-life activities. Neurobiol Aging 2018;70:180-183.
10. Hebert LE, Weuve J, Scherr PA, Evans DA. Alzheimer disease in the United States (2010-2050) estimated using the 2010 census. Neurology 2013;80:1778-1783.
11. Hebert LE, Bienias JL, Aggarwal NT, et al. Change in risk of Alzheimer disease over time. Neurology 2010;75:786-791.
12. Kim J, Basak JM, Holtzman DM. The role of apolipoprotein E in Alzheimer's disease. Neuron 2009;63:287-303.
13. Moreno-Grau S, de Rojas I, Hernandez I, et al. Genome-wide association analysis of dementia and its clinical endophenotypes reveal novel loci associated with Alzheimer's disease and three causality networks. The GR@ACE project: Alzheimers Dement 2019;15:1333-1347.
14. Jansen IE, Savage JE, Watanabe K, et al. Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer's disease risk. Nat Genet 2019;51:404-413.
15. Braithwaist C, Anttila V, Bulik-Sullivan B, et al. Analysis of shared heritability in common disorders of the brain. Science 2018;360.
16. Sudlow C, Gallacher J, Allen N, et al. UK Biobank: An Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age. PLoS medicine 2015;12:e1001779.
17. Bycroft C, Freeman C, Petkova D, et al. The UK Biobank resource with deep phenotyping and genomic data. Nature 2018;562:203-209.
18. Power MC, Weuve J, Sharrett AR, Blacker D, Gottesman RF. Statins, cognition, and dementia—systematic review and methodological commentary. Nature reviews Neurology 2015;11:220-229.
19. Yoon SJ, Suh SY, Lee YJ, et al. Prospective Validation of Objective Prognostic Score for Advanced Cancer Inpatients in South Korea: a Multicenter Study. Journal of palliative medicine 2017;20:65-68.
20. Najar J, Ostling S, Gudmundsson P, et al. Cognitive and physical activity and dementia: A 44-year longitudinal population study of women. Neurology 2019;92:e1322-e1330.
21. Wilkinson T, Schnier C, Bush K, et al. Identifying dementia outcomes in UK Biobank: a validation study of primary care, hospital admissions and mortality data. European journal of epidemiology 2019;34:557-565.
22. Lambert JC, Ibrahim-Verbaas CA, Harold D, et al. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. Nat Genet 2013;45:1452-1458.

Copyright © 2022 American Academy of Neurology. Unauthorized reproduction of this article is prohibited
23. Seripa D, D’Onofrio G, Panza F, Cascavilla L, Masullo C, Pilotto A. The genetics of the human APOE polymorphism. Rejuvenation research 2011;14:491-500.
24. Townsend PP, Beatie A. Health and deprivation: inequality and the North: Routledge1988.
25. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sørensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. BMC Med Res Methodol 2011;11:83.
26. Fawns-Ritchie C, Deary IJ. Reliability and validity of the UK Biobank cognitive tests. PLoS One 2020;15:e0231627.
27. Jannasch F, Riordan F, Andersen LF, Schulze MB. Exploratory dietary patterns: a systematic review of methods applied in pan-European studies and of validation studies. The British journal of nutrition 2018;120:601-611.
28. Weuve J, Proust-Lima C, Power MC, et al. Guidelines for reporting methodological challenges and evaluating potential bias in dementia research. Alzheimers Dement 2015;11:1098-1109.
29. Hamer M, Chida Y. Physical activity and risk of neurodegenerative disease: a systematic review of prospective evidence. Psychol Med 2009;39:3-11.
30. Sofi F, Valeyev D, Bacci D, et al. Physical activity and risk of cognitive decline: a meta-analysis of prospective studies. J Intern Med 2011;269:107-117.
31. Sabia S, Dugravot A, De Stavola B, et al. Physical activity, cognitive decline, and risk of dementia: 28 year follow-up of Whitehall II cohort study. BMJ 2017;357:j2709.
32. Young J, Angevaren M, Rusted J, Tabet N. Aerobic exercise to improve cognitive function in older people without known cognitive impairment. The Cochrane database of systematic reviews 2015:CD005381.
33. Oja P, Kelly P, Pedisic Z, et al. Associations of specific types of sports and exercise with all-cause and cardiovascular-disease mortality: a cohort study of 80 306 British adults. Br J Sports Med 2017;51:812-817.
34. Christoforetti G, Oliani MM, Gobbi S, Stella F, Bucen Gobbi LT, Renato Canineu P. A controlled clinical trial on the effects of motor intervention on balance and cognition in institutionalized elderly patients with dementia. Clinical rehabilitation 2008;22:618-626.
35. Lamb SE, Sheehan B, Atherton N, et al. Dementia And Physical Activity (DAPA) trial of moderate to high intensity exercise training for people with dementia: randomised controlled trial. BMJ (Clinical research ed) 2018;361:k1675.
36. Caamaño-Isorna F, Corral M, Montes-Martínez A, Takkouche B. Education and dementia: a meta-analytic study. Neuroepidemiology 2006;26:226-232.
37. Loprinzi PD, Frith E. A brief primer on the mediational role of BDNF in the exercise-memory link. Clin Physiol Funct Imaging 2019;39:9-14.
38. Nascimento CM, Pereira JR, de Andrade LP, et al. Physical exercise in MCI elderly promotes reduction of pro-inflammatory cytokines and improvements on cognition and BDNF peripheral levels. Curr Alzheimer Res 2014;11:799-805.
39. Ainslie PN, Cotter JD, George KP, et al. Elevation in cerebral blood flow velocity with aerobic fitness throughout healthy human ageing. J Physiol 2008;586:4005-4010.
40. de Sousa CV, Sales MM, Rosa TS, Lewis JE, de Andrade RV, Simoes HG. The Antioxidant Effect of Exercise, A Systematic Review and Meta-Analysis. Sports Med 2017;47:277-293.
41. Rottkamp CA, Nunomura A, Raina AK, Sayre LM, Perry G, Smith MA. Oxidative stress, antioxidants, and Alzheimer disease. Alzheimer Dis Assoc Disord 2000;14 Suppl 1:S62-66.
42. Jensen CS, Hasselbalch SG, Waldemar G, Simonsen AH. Biochemical Markers of Physical Exercise on Mild Cognitive Impairment and Dementia: Systematic Review and Perspectives. Front Neurol 2015;6:187.
43. Brown BM, Peiffer JJ, Martins RN. Multiple effects of physical activity on molecular and cognitive signs of brain aging: can exercise slow neurodegeneration and delay Alzheimer's disease? Mol Psychiatry 2013;18:864-874.
44. Kuiper JS, Zuidersma M, Oude Voshaar RC, et al. Social relationships and risk of dementia: A systematic review and meta-analysis of longitudinal cohort studies. Ageing research reviews 2015;22:39-57.
45. Hemingway H, Marmot M. Evidence based cardiology: psychosocial factors in the aetiology and prognosis of coronary heart disease. Systematic review of prospective cohort studies. BMJ 1999;318:1460-1467.
46. Santini ZI, Koyanagi A, Tyrovolas S, Mason C, Haro JM. The association between social relationships and depression: a systematic review. J Affect Disord 2015;175:53-65.
47. Fry A, Littlejohns TJ, Sudlow C, et al. Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general population. American journal of...
48. Sudlow C, Gallacher J, Allen N, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS medicine 2015;12:e1001779.

49. Batty GD, Gale CR, Kivimaki M, Deary IJ, Bell S. Comparison of risk factor associations in UK Biobank against representative, general population based studies with conventional response rates: prospective cohort study and individual participant meta-analysis. BMJ 2020;368:m131.
Table 1. Characteristics of the study cohort, by the presence of any or specific subtypes of dementia status during follow-up

| Characteristics                              | Dementia-free | Dementia | Vascular dementia | Alzheimer's disease | Other dementia |
|----------------------------------------------|---------------|----------|-------------------|---------------------|---------------|
|                                             | N=496,191     | N=5,185  | N=803             | N=1,561             | N=2,697       |
| Age at baseline (y), mean (SD)              | 56.45(8.08)   | 64.17(4.90) | 64.79(4.40) | 64.51(4.28) | 63.95(5.23) |
| Follow up time (y), mean (SD)               | 10.69(1.47)   | 7.90(2.59) | 7.94(2.60) | 7.95(2.51) | 7.86(2.64) |
| Sex (%)                                      |               |          |                   |                     |               |
| Female                                       | 270400(54.5) | 2421(46.7) | 332(41.3) | 819(52.5) | 1216(45.1) |
| Male                                         | 225791(45.5) | 2764(53.3) | 471(58.7) | 742(47.5) | 1481(54.9) |
| Race and ethnicity* (%)                     |               |          |                   |                     |               |
| White                                        | 467604(94.2) | 4937(95.2) | 765(95.3) | 1499(96.0) | 2554(94.7) |
| Asian                                        | 11359(2.3)   | 84(1.6) | 16(2.0) | 22(1.4) | 49(1.8) |
| Black                                        | 7969(1.6)    | 88(1.7) | 4(0.5) | 22(1.4) | 48(1.8) |
| Mixed                                        | 2933(0.6)    | 22(0.4) | 0(0) | 7(0.4) | 11(0.4) |
| Unknown                                      | 1800(0.4)    | 25(0.5) | 2(0.2) | 5(0.3) | 18(0.7) |
| Townsend deprivation index, mean (SD)       | -1.30(3.09)  | -0.85(3.35) | -0.58(3.52) | -1.12(3.24) | -0.76(3.37) |
| Income, n (%)                                |               |          |                   |                     |               |
| <£18,000                                     | 95346(19.2)  | 1799(34.7) | 320(39.9) | 523(33.5) | 928(34.4) |
| £18,000-£30,999                              | 106982(21.6) | 1167(22.5) | 160(19.9) | 363(23.3) | 616(22.8) |
| £31,000-£51,999                              | 110204(22.2) | 543(10.5) | 75(9.3) | 160(10.2) | 291(10.8) |
| £52,000-£100,000                             | 86002(17.3)  | 247(4.8) | 32(4.0) | 66(4.2) | 132(4.9) |
| >£100,000                                    | 22866(4.6)   | 61(1.2) | 6(0.7) | 16(1.0) | 33(1.2) |
| Unknown                                      | 74791(15.1)  | 1368(26.4) | 210(26.2) | 433(27.7) | 697(25.8) |
| Education: college/university degree         |               |          |                   |                     |               |
| Yes                                          | 160112(32.3) | 1007(19.4) | 124(15.4) | 291(18.6) | 547(20.3) |
| No                                           | 243726(49.1) | 2142(41.3) | 329(41.0) | 670(42.9) | 1091(40.5) |
| Unknown                                      | 92353(18.6)  | 2036(39.3) | 350(43.6) | 600(38.4) | 1059(39.3) |
| Body mass index, kg/m², n (%)                |               |          |                   |                     |               |
| <18.5                                        | 2456(0.5)     | 37(0.7) | 7(0.9) | 7(0.4) | 22(0.8) |
| 18.5-24.9                                    | 158272(31.9) | 1506(29.0) | 183(22.8) | 491(31.5) | 784(29.1) |
| 25-29.9                                      | 210911(42.5) | 2126(41.0) | 303(37.7) | 671(43.0) | 1111(41.2) |
| ≥30                                          | 121885(24.6) | 1449(27.9) | 300(37.4) | 380(24.3) | 739(27.4) |
| Unknown                                      | 2667(0.5)    | 67(1.3) | 10(1.2) | 12(0.8) | 41(1.5) |
| Smoking status, n (%)                        |               |          |                   |                     |               |
| Never                                        | 271080(54.6) | 2357(45.5) | 318(39.6) | 765(49.0) | 1214(45.0) |
| Previous                                     | 170789(34.4) | 2207(42.6) | 377(46.9) | 652(41.8) | 1127(41.8) |
| Current                                      | 52370(10.6)  | 580(11.2) | 101(12.6) | 131(8.4) | 335(12.4) |
| Unknown                                      | 1952(0.4)    | 41(0.8) | 7(0.9) | 13(0.8) | 21(0.8) |
| Alcohol status, n (%)                        |               |          |                   |                     |               |
| Never                                        | 21996(4.4)   | 370(7.1) | 60(7.5) | 116(7.4) | 190(7.0) |
| Previous                                     | 17697(3.6)   | 393(7.6) | 71(8.8) | 99(6.3) | 214(7.9) |
| Current                                      | 455819(91.9) | 4405(85.0) | 668(83.2) | 1340(85.8) | 2286(84.8) |
| Unknown       | 679(0.1) | 17(0.3) | 4(0.5) | 6(0.4) | 7(0.3) |
|--------------|----------|---------|--------|--------|--------|
| **Charlson comorbidity index, n (%)** |          |         |        |        |        |
| 0            | 433715(87.4) | 3747(72.3) | 471(58.7) | 1207(77.3) | 1965(72.9) |
| ≥1           | 62476(12.6)  | 1438(27.7)  | 332(41.3)  | 354(22.7)  | 732(27.1)  |
| **History of hypertension, n (%)** |          |         |        |        |        |
| Yes          | 50163(10.1)  | 1267(24.4)  | 298(37.1)  | 334(21.4)  | 620(23.0)  |
| No           | 446028(89.9) | 3918(75.6)  | 505(62.9)  | 1227(78.6) | 2077(77.0) |
| **History of hyperlipidemia, n (%)** |          |         |        |        |        |
| Yes          | 73031(14.7)  | 1544(29.8)  | 304(37.9)  | 440(28.2)  | 785(29.1)  |
| No           | 423160(85.3) | 3641(70.2)  | 499(62.1)  | 1121(71.8) | 1912(70.9) |
| **Family history of dementia, n (%)** |          |         |        |        |        |
| Yes          | 57342(11.6)  | 1063(20.5)  | 150(18.7)  | 404(25.9)  | 482(17.9)  |
| No           | 349149(70.4) | 2624(50.6)  | 394(49.1)  | 749(48.0)  | 1416(52.5) |
| Unknown      | 89700(18.1)  | 1498(28.9)  | 259(32.3)  | 408(26.1)  | 799(29.6)  |

*The specific numbers and percentages for categories that so small as to potentially identify study participants were not reported.*
Figure legends

Figure 1 Flow chart of the study

'Caucasian ancestry refers to a genetic ethnic group, involving individuals who self-identified as 'White British' and have very similar genetic ancestry based on a principal components analysis of the genotypes.'
Figure 2 Hazard ratios (HRs) for the associations between all items of physical and mental activity and dementia

*Watching TV was regarded as a continues variable.

†HRs were derived from Cox regression models, adjusted for age, sex, race and ethnicity, Townsend deprivation index, income, body mass index, smoking status, alcohol status, Charlson comorbidity index, history of hypertension, history of hyperlipidemia, and family history of dementia.
Figure 3 Associations between physical activity patterns and any or specific subtypes of dementia

CI, confidence interval; IR, incidence rate; HR, hazard ratio; Ref, reference.

*HRs and 95% CIs were derived from Cox regression models, adjusted for age, sex, race and ethnicity, Townsend deprivation index, education, income, body mass index, smoking status, alcohol status, Charlson comorbidity index, history of hypertension, history of hyperlipidemia, and family history of dementia.
| Principal components of physical activity | Number of cases/1,000 person-years (RR) | HR (95%CI)* | Number of cases/1,000 person-years (RR) | HR (95%CI)* |
|------------------------------------------|----------------------------------------|-------------|----------------------------------------|-------------|
| **Dementia**                             |                                        |             |                                        |             |
| **PC1** related to "vigoroues and other exercise at leisure time" |                                        |             |                                        |             |
| Low (<1st tertile)                      | 2.073/1,302.68 (1.59)                  | Reference   | 3.33/1,302.68 (0.26)                   | Reference   |
| Moderate (1st–2nd tertile)              | 1.03/1,313.4 (0.79)                   | 0.75 (0.70–0.81) | 153/1,313.4 (0.12)                   | 0.77 (0.63–0.93) |
| High (2nd–4th tertile)                  | 0.65 (0.59–0.71)                      |             | 821/1,333.82 (0.06)                   | 0.67 (0.52–0.87) |
| **PC2** related to "housework-related activity" |                                        |             |                                        |             |
| Low (<1st tertile)                      | 1.35/1,320.6 (1.02)                   | Reference   | 215/1,320.6 (0.16)                    | Reference   |
| Moderate (1st–2nd tertile)              | 1.22/1,309.45 (0.93)                  | 0.91 (0.85–0.99) | 194/1,309.45 (0.15)                  | 0.95 (0.78–1.16) |
| High (2nd–4th tertile)                  | 1.13/1,319.86 (0.86)                  | 0.79 (0.72–0.85) | 159/1,319.86 (0.12)                  | 0.75 (0.60–0.93) |
| **PC3** related to "transport-related activity" |                                        |             |                                        |             |
| Low (<1st tertile)                      | 0.7/1,326.03 (0.51)                   | 1.10 (1.00–1.21) | 112/1,326.03 (0.08)                   | 1.00 (0.79–1.26) |
| Moderate (1st–2nd tertile)              | 1.32/1,321 (0.02)                     | 1.10 (1.00–1.21) | 240/1,321 (0.18)                     | 0.92 (0.72–1.16) |
| High (2nd–4th tertile)                  | 1.82/1,320.87 (1.29)                  |             |                                        |             |
| **PC4** related to "job-related activity" |                                        |             |                                        |             |
| Low (<1st tertile)                      | 1.43/1,310.68 (1.1)                   | 1.05 (0.98–1.13) | 252/1,310.68 (0.19)                   | 0.93 (0.77–1.12) |
| Moderate (1st–2nd tertile)              | 1.49/1,312.94 (1.1)                   | 0.99 (0.98–1.00) | 216/1,312.94 (0.16)                  | 0.93 (0.77–1.12) |
| High (2nd–4th tertile)                  | 1.03/1,326.28 (0.62)                  |             |                                        |             |
| **PC5** related to "walking for pleasure" |                                        |             |                                        |             |
| Low (<1st tertile)                      | 1.23/1,312.24 (0.94)                  | 1.00 (0.92–1.08) | 209/1,312.24 (0.16)                  | 0.83 (0.68–1.01) |
| Moderate (1st–2nd tertile)              | 1.29/1,308.8 (0.99)                   | 1.07 (0.99–1.16) | 173/1,308.8 (0.13)                   | 1.09 (0.85–1.33) |
| High (2nd–4th tertile)                  | 1.78/1,331.86 (0.88)                  |             |                                        |             |

### Alzheimer disease

| Principal components of physical activity | Number of cases/1,000 person-years (RR) | HR (95%CI)* | Number of cases/1,000 person-years (RR) | HR (95%CI)* |
|------------------------------------------|----------------------------------------|-------------|----------------------------------------|-------------|
| **PC1** related to "vigoroues and other exercise at leisure time" |                                        |             |                                        |             |
| Low (<1st tertile)                      | 613/1,302.68 (0.47)                   | 0.79 (0.70–0.89) | 106/1,302.68 (0.83)                   | Reference   |
| Moderate (1st–2nd tertile)              | 328/1,313.4 (0.25)                    | 0.71 (0.66–0.84) | 552/1,313.4 (0.41)                   | 0.73 (0.66–0.81) |
| High (2nd–4th tertile)                  | 193/1,333.82 (0.14)                  |             | 309/1,333.82 (0.23)                   | 0.61 (0.53–0.70) |
| **PC2** related to "housework-related activity" |                                        |             |                                        |             |
| Low (<1st tertile)                      | 427/1,320.6 (0.32)                   | 0.82 (0.71–0.94) | 344/1,320.6 (0.32)                   | 0.80 (0.70–0.94) |
| Moderate (1st–2nd tertile)              | 427/1,320.6 (0.32)                   | 0.82 (0.71–0.94) | 344/1,320.6 (0.32)                   | 0.80 (0.70–0.94) |
| High (2nd–4th tertile)                  | 369/1,319.86 (0.28)                  |             | 581/1,319.86 (0.44)                   | 0.80 (0.71–0.89) |
| **PC3** related to "transport-related activity" |                                        |             |                                        |             |
| Low (<1st tertile)                      | 180/1,326.03 (0.14)                  | 1.16 (0.97–1.38) | 359/1,326.03 (0.27)                  | 1.12 (0.98–1.27) |
| Moderate (1st–2nd tertile)              | 414/1,321 (0.31)                     | 1.14 (0.96–1.37) | 669/1,321 (0.52)                     | 1.17 (0.96–1.26) |
| High (2nd–4th tertile)                  | 533/1,320.87 (0.41)                  |             | 873/1,320.87 (0.67)                   | 1.20 (0.98–1.27) |
| **PC4** related to "job-related activity" |                                        |             |                                        |             |
| Low (<1st tertile)                      | 429/1,316.88 (0.33)                  | 1.14 (0.96–1.37) | 733/1,316.88 (0.56)                  | 1.17 (0.96–1.26) |
| Moderate (1st–2nd tertile)              | 429/1,316.88 (0.33)                  | 1.14 (0.96–1.37) | 733/1,316.88 (0.56)                  | 1.17 (0.96–1.26) |
| High (2nd–4th tertile)                  | 257/1,326.28 (0.19)                  |             | 434/1,326.28 (0.33)                   | 0.96 (0.85–1.08) |
| **PC5** related to "walking for pleasure" |                                        |             |                                        |             |
| Low (<1st tertile)                      | 328/1,312.24 (0.25)                  | 1.18 (1.02–1.37) | 674/1,312.24 (0.51)                  | 0.98 (0.85–1.05) |
| Moderate (1st–2nd tertile)              | 421/1,365.8 (0.32)                   | 1.29 (1.11–1.49) | 636/1,365.8 (0.51)                   | 0.98 (0.85–1.05) |
| High (2nd–4th tertile)                  | 385/1,331.86 (0.29)                  |             | 566/1,331.86 (0.44)                   | 0.96 (0.85–1.08) |
Figure 4 Associations between mental activity patterns and any or specific subtypes of dementia

CI, confidence interval; IR, incidence rate; HR, hazard ratio; Ref, reference.

*HRs and 95% CIs were derived from Cox regression models, adjusted for age, sex, race and ethnicity, Townsend deprivation index, education, income, body mass index, smoking status, alcohol status, Charlson comorbidity index, history of hypertension, history of hyperlipidemia, and family history of dementia.

| Principal components of physical activity | Dementia | Vascular dementia |
|-----------------------------------------|----------|------------------|
|                                        | Number of cases/1,000 person-years (IR) | HR (95%CI)* | Number of cases/1,000 person-years (IR) | HR (95%CI)* |
| PC1, more related to "pub or social club visit" | | | |
| Low (<1st tertile) | 509/750.35 (0.68) | Reference | 509/750.35 (0.07) | Reference |
| Moderate (1st–2nd tertile) | 494/709.04 (0.70) | 1.05 (0.92–1.20) | 77/709.54 (0.11) | 1.62 (1.12–2.35) |
| High (2nd–3rd tertile) | 501/784.19 (0.77) | 1.08 (0.94–1.25) | 96/784.19 (0.12) | 1.70 (1.15–2.52) |
| PC2, more related to "watching TV" | | | |
| Low (<1st tertile) | 279/747.25 (0.37) | Reference | 34/747.25 (0.05) | Reference |
| Moderate (1st–2nd tertile) | 465/754.07 (0.62) | 1.00 (0.86–1.17) | 69/754.97 (0.09) | 1.15 (0.75–1.75) |
| High (2nd–3rd tertile) | 810/742.27 (1.09) | 1.05 (0.90–1.23) | 120/742.27 (0.16) | 1.11 (0.72–1.70) |
| PC3, more related to "attending other group activity/ adult education classes" | | | |
| Low (<1st tertile) | 607/745.45 (0.81) | Reference | 7/745.45 (0.11) | Reference |
| Moderate (1st–2nd tertile) | 419/750.19 (0.56) | 0.89 (0.79–0.99) | 66/750.19 (0.09) | 0.99 (0.78–1.32) |
| High (2nd–3rd tertile) | 528/765.95 (0.71) | 0.96 (0.85–1.08) | 81/765.95 (0.11) | 1.19 (0.86–1.63) |
| PC4, more related to "friend/family visit" | | | |
| Low (<1st tertile) | 601/746.65 (0.8) | Reference | 92/746.65 (0.12) | Reference |
| Moderate (1st–2nd tertile) | 491/746.28 (0.66) | 0.87 (0.77–0.98) | 65/746.28 (0.09) | 0.76 (0.55–1.05) |
| High (2nd–3rd tertile) | 462/746.65 (0.62) | 0.85 (0.75–0.96) | 66/746.65 (0.09) | 0.82 (0.60–1.13) |

| Alzheimer disease | Number of cases/1,000 person-years (IR) | HR (95%CI)* | Number of cases/1,000 person-years (IR) | HR (95%CI)* |
|-------------------|----------------------------------------|-------------|----------------------------------------|-------------|
| PC1, more related to "pub or social club visit" | | | |
| Low (<1st tertile) | 166/750.35 (0.22) | Reference | 274/750.35 (0.37) | Reference |
| Moderate (1st–2nd tertile) | 150/709.04 (0.21) | 1.01 (0.80–1.27) | 247/709.04 (0.35) | 0.95 (0.79–1.14) |
| High (2nd–3rd tertile) | 163/784.19 (0.21) | 1.10 (0.86–1.41) | 277/784.19 (0.35) | 0.96 (0.79–1.17) |
| PC2, more related to "watching TV" | | | |
| Low (<1st tertile) | 79/747.25 (0.11) | Reference | 146/747.25 (0.2) | Reference |
| Moderate (1st–2nd tertile) | 140/754.07 (0.19) | 1.00 (0.75–1.33) | 247/754.07 (0.33) | 1.04 (0.84–1.28) |
| High (2nd–3rd tertile) | 260/742.27 (0.35) | 1.07 (0.80–1.42) | 405/742.27 (0.55) | 1.05 (0.84–1.30) |
| PC3, more related to "attending other group activity/ adult education classes" | | | |
| Low (<1st tertile) | 198/745.45 (0.26) | Reference | 322/745.45 (0.43) | Reference |
| Moderate (1st–2nd tertile) | 125/750.19 (0.17) | 0.85 (0.67–1.07) | 206/750.19 (0.27) | 0.82 (0.60–0.99) |
| High (2nd–3rd tertile) | 156/765.95 (0.21) | 0.86 (0.69–1.07) | 271/765.95 (0.36) | 0.95 (0.80–1.12) |
| PC4, more related to "friend/family visit" | | | |
| Low (<1st tertile) | 171/746.65 (0.23) | Reference | 315/746.65 (0.42) | Reference |
| Moderate (1st–2nd tertile) | 166/746.28 (0.22) | 1.01 (0.82–1.25) | 245/746.28 (0.33) | 0.84 (0.71–1.00) |
| High (2nd–3rd tertile) | 142/746.65 (0.19) | 0.88 (0.71–1.17) | 238/746.65 (0.32) | 0.85 (0.71–1.00) |
Figure 5 Associations of physical and mental activity patterns with dementia among individuals with different levels of disease susceptibility

CI, confidence interval; IR, incidence rate; HR, hazard ratio; PRS, polygenic risk score; Ref, reference

HRs and 95% CIs were derived from Cox regression models, adjusted for age, sex, race and ethnicity, Townsend deprivation index, education, income, body mass index, smoking status, alcohol status, Charlson comorbidity index, history of hypertension, and history of hyperlipidemia.

| Principal components | Low genetic risk (PRS<1st tertile) | High genetic risk (PRS>2nd tertile) |
|----------------------|-----------------------------------|-----------------------------------|
|                      | Number of cases/1,000 person-years (IR) | HR (95%CI)* | Number of cases/1,000 person-years (IR) | HR (95%CI)* |
| Physical activity    |                                   |                                   |                                   |
| PC1 more related to  |                                   |                                   |                                   |
| "vigorous and other  |                                   |                                   |                                   |
| exercise at leisure" |                                   |                                   |                                   |
| Low (<1st tertile)   | 466/325 (1.4)                    | Reference                          | 664/327 (2.0)                    | Reference                          |
| Mod (<1st tertile)   | 22/138 (8.6)                     | 0.89 (0.59-1.31)                  | 0.84 (0.54-1.30)                 | 0.68 (0.47-0.97)                  |
| High (>2nd tertile)  | 543/347.5 (1.4)                  | 1.14 (0.93-1.38)                  | 463/341 (1.35)                   | 0.55 (0.38-0.79)                  |
| PC2 more related to  |                                   |                                   |                                   |
| "housework-related activity" |                   |                                   |                                   |
| Low (<1st tertile)   | 303/314 (1.0)                    | Reference                          | 433/315 (1.3)                    | Reference                          |
| Mod (<1st tertile)   | 27/106 (9.6)                     | 0.89 (0.52-1.51)                  | 423/319 (1.25)                   | 0.69 (0.39-1.20)                  |
| High (>2nd tertile)  | 269/373 (1.2)                    | 0.76 (0.44-1.30)                  | 497/355 (1.15)                   | 0.24 (0.05-0.96)                  |
| PC3 more related to  |                                   |                                   |                                   |
| "transport-related activity" |                  |                                   |                                   |
| Low (<1st tertile)   | 152/337 (5.0)                    | Reference                          | 236/336 (8.2)                    | Reference                          |
| Mod (<1st tertile)   | 363/342 (1.5)                    | 1.14 (0.93-1.38)                  | 463/341 (1.35)                   | 0.55 (0.38-0.79)                  |
| High (>2nd tertile)  | 377/332 (1.1)                    | 1.18 (0.97-1.45)                  | 563/331 (1.7)                    | 1.04 (0.88-1.22)                  |
| PC4 more related to  |                                   |                                   |                                   |
| "job-related activity" |                                     |                                   |                                   |
| Low (<1st tertile)   | 323/342 (1.2)                    | Reference                          | 504/343 (1.4)                    | Reference                          |
| Mod (<1st tertile)   | 323/342 (1.5)                    | 1.07 (0.92-1.25)                  | 499/342 (1.4)                    | 1.05 (0.85-1.31)                  |
| High (>2nd tertile)  | 186/356 (1.1)                    | 1.00 (0.83-1.20)                  | 259/316 (0.79)                   | 0.93 (0.60-1.49)                  |
| PC5 more related to  |                                   |                                   |                                   |
| "walking for pleasure" |                                     |                                   |                                   |
| Low (<1st tertile)   | 292/326 (1.3)                    | Reference                          | 408/324 (1.2)                    | Reference                          |
| Mod (<1st tertile)   | 25/235 (1.0)                     | 0.85 (0.71-1.00)                  | 465/326 (1.39)                   | 1.03 (0.90-1.18)                  |
| High (>2nd tertile)  | 288/335 (1.0)                    | 1.11 (0.94-1.31)                  | 385/346 (1.1)                    | 1.01 (0.87-1.15)                  |
| Mental activity      |                                   |                                   |                                   |
| PC1 more related to  |                                   |                                   |                                   |
| "pub or social club visit" |                                |                                   |                                   |
| Low (<1st tertile)   | 109/181 (2.3)                    | Reference                          | 165/184 (0.9)                    | Reference                          |
| Mod (<1st tertile)   | 11/178 (1.3)                     | 1.11 (0.84-1.47)                  | 15/171 (1.4)                     | 1.03 (0.82-1.29)                  |
| High (>2nd tertile)  | 122/205 (1.2)                    | 1.18 (0.87-1.60)                  | 182/196 (0.98)                   | 1.04 (0.82-1.31)                  |
| PC2 more related to  |                                   |                                   |                                   |
| "watching TV"        |                                   |                                   |                                   |
| Low (<1st tertile)   | 66/184 (2.4)                     | Reference                          | 89/184 (2.4)                     | Reference                          |
| Mod (<1st tertile)   | 104/190 (3.1)                    | 1.00 (0.73-1.38)                  | 152/192 (0.72)                   | 0.98 (0.75-1.24)                  |
| High (>2nd tertile)  | 181/192 (1.4)                    | 1.13 (0.82-1.56)                  | 263/192 (1.3)                    | 1.02 (0.77-1.34)                  |
| PC3 more related to  |                                   |                                   |                                   |
| "attending other group activity" |                              |                                   |                                   |
| Low (<1st tertile)   | 127/180 (1.2)                    | Reference                          | 183/183 (0.7)                    | Reference                          |
| Mod (<1st tertile)   | 99/149 (1.5)                     | 0.90 (0.69-1.20)                  | 157/139 (0.4)                    | 1.02 (0.83-1.27)                  |
| High (>2nd tertile)  | 125/193 (1.0)                    | 0.98 (0.66-1.46)                  | 164/192 (0.85)                   | 0.93 (0.75-1.15)                  |
| PC4 more related to  |                                   |                                   |                                   |
| "friends visit"      |                                   |                                   |                                   |
| Low (<1st tertile)   | 121/180 (1.0)                    | Reference                          | 164/181 (0.8)                    | Reference                          |
| Mod (<1st tertile)   | 122/190 (1.1)                    | 0.99 (0.77-1.30)                  | 164/191 (0.85)                   | 0.84 (0.68-1.04)                  |
| High (>2nd tertile)  | 109/155 (1.5)                    | 0.89 (0.69-1.16)                  | 146/194 (0.75)                   | 0.74 (0.51-1.09)                  |
Figure 6 Associations of physical and mental activity patterns with dementia among individuals with and without a self-reported family history of dementia

CI, confidence interval; IR, incidence rate; HR, hazard ratio; Ref, reference

HRs and 95% CIs were derived from Cox regression models, adjusted for age, sex, race and ethnicity, Townsend deprivation index, education, income, body mass index, smoking status, alcohol status, Charlson comorbidity index, history of hypertension, and history of hyperlipidemia.

| Principal components | Without family history | With family history |
|----------------------|------------------------|---------------------|
|                      | Number of cases/1,000 person-years (IR) | HR (95%CI) * | Number of cases/1,000 person-years (IR) | HR (95%CI) * |
| **Physical activity** |                        |                     |                                   |                     |
| PC1, more related to "vigor and other exercise at leisure time" |                        |                     |                                   |                     |
| Low (1st tertile) | 1,043/888.73 (1.17) | Reference | 418/162.69 (2.57) | Reference |
| Middle (2nd tertile) | 547/954.92 (1.08) | 0.69 (0.60-0.78) | 249/174.91 (1.59) | 0.85 (0.72-1.00) |
| High (3rd tertile) | 349/1,001.19 (0.35) | 1.00 (0.98-1.02) | 124/38.86 (0.89) | 0.64 (0.52-0.79) |
| PC2, more related to "housework-related activity" |                        |                     |                                   |                     |
| Low (1st tertile) | 698/932.23 (0.75) | Reference | 272/143.31 (1.9) | Reference |
| Moderate (2nd tertile) | 641/944.61 (0.68) | 0.89 (0.80-0.99) | 278/150.75 (1.84) | 0.94 (0.80-1.12) |
| High (3rd tertile) | 600/955.5 (0.63) | 1.06 (0.95-1.21) | 237/151.79 (1.46) | 0.72 (0.60-0.87) |
| PC3, more related to "transport-related activity" |                        |                     |                                   |                     |
| Low (1st tertile) | 359/963.01 (0.37) | Reference | 124/127.85 (0.97) | Reference |
| Moderate (2nd tertile) | 717/952.99 (0.75) | 1.10 (0.96-1.25) | 274/156.41 (1.75) | 1.09 (0.86-1.41) |
| High (3rd tertile) | 863/915.84 (0.94) | 1.06 (0.93-1.21) | 389/171.59 (2.37) | 1.20 (0.97-1.49) |
| PC4, more related to "job-related activity" |                        |                     |                                   |                     |
| Low (1st tertile) | 628/926.71 (0.68) | Reference | 262/147.07 (1.78) | Reference |
| Moderate (2nd tertile) | 686/935.73 (0.77) | 1.00 (0.90-1.12) | 280/157.71 (1.78) | 1.04 (0.84-1.32) |
| High (3rd tertile) | 467/997.46 (0.62) | 1.08 (0.97-1.21) | 295/151.04 (1.42) | 1.01 (0.87-1.24) |
| **Mental activity** |                        |                     |                                   |                     |
| PC1, more related to "pub or social club visit" |                        |                     |                                   |                     |
| Low (1st tertile) | 307/858.86 (0.55) | Reference | 111/92.86 (1.2) | Reference |
| Moderate (2nd tertile) | 254/525.04 (0.48) | 0.91 (0.76-1.09) | 123/79.41 (1.55) | 1.28 (0.98-1.67) |
| High (3rd tertile) | 301/566.32 (0.53) | 1.03 (0.86-1.24) | 118/86.29 (1.37) | 1.13 (0.84-1.52) |
| PC2, more related to "watching TV" |                        |                     |                                   |                     |
| Low (1st tertile) | 163/571.09 (0.29) | Reference | 48/75.14 (0.64) | Reference |
| Moderate (2nd tertile) | 176/556.71 (0.47) | 1.00 (0.81-1.22) | 122/87.36 (1.29) | 1.33 (0.94-1.88) |
| High (3rd tertile) | 437/523.83 (0.83) | 1.03 (0.83-1.26) | 192/96.06 (1.2) | 1.39 (0.98-1.99) |
| PC3, more related to "attending other group activity/ adult education classes" |                        |                     |                                   |                     |
| Low (1st tertile) | 327/549.1 (0.6) | Reference | 142/87.19 (0.63) | Reference |
| Moderate (2nd tertile) | 242/557.63 (0.43) | 0.96 (0.81-1.13) | 82/82.11 (1.01) | 0.76 (0.57-1.00) |
| High (3rd tertile) | 293/544.49 (0.54) | 0.99 (0.84-1.17) | 126/89.28 (1.43) | 0.98 (0.77-1.25) |
| PC4, more related to "friends visits" |                        |                     |                                   |                     |
| Low (1st tertile) | 324/525.06 (0.6) | Reference | 135/81.83 (1.7) | Reference |
| Moderate (2nd tertile) | 268/553.55 (0.48) | 0.86 (0.73-1.01) | 11/100.74 (1.77) | 0.77 (0.60-0.94) |
| High (3rd tertile) | 270/561.82 (0.48) | 0.88 (0.75-1.03) | 103/89.99 (1.14) | 0.72 (0.56-0.93) |
Physical and Mental Activity, Disease Susceptibility, and Risk of Dementia: A Prospective Cohort Study Based on UK Biobank
Jianwei Zhu, Fenfen Ge, Yu Zheng, et al.
Neurology published online July 27, 2022
DOI 10.1212/WNL.0000000000200701

This information is current as of July 27, 2022

Updated Information & Services
including high resolution figures, can be found at:
http://n.neurology.org/content/early/2022/07/26/WNL.0000000000200701.full

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
All Cognitive Disorders/Dementia
http://n.neurology.org/cgi/collection/all_cognitive_disorders_dementia
Alzheimer's disease
http://n.neurology.org/cgi/collection/alzheimers_disease
Association studies in genetics
http://n.neurology.org/cgi/collection/association_studies_in_genetics
Cohort studies
http://n.neurology.org/cgi/collection/cohort_studies

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://www.neurology.org/about/about_the_journal#permissions

Reprints
Information about ordering reprints can be found online:
http://n.neurology.org/subscribers/advertise