Title Page

Prospective associations of exercise and depressive symptoms in older adults:

The role of apolipoprotein E4

Po-Wen Ku, Andrew Steptoe, Li-Jung Chen*

Running title: Exercise, APOE-e4 and depressive symptoms

1st author: Po-Wen Ku, PhD (Exercise and Health); PhD (Epidemiology)
Graduate Institute of Sports and Health, National Changhua University of Education, Changhua City, Taiwan
Department of Epidemiology and Public Health, University College London, London, UK
E-mail: powen.ku@gmail.com

2nd author: Andrew Steptoe, DPhil, DSc
Department of Epidemiology and Public Health, University College London, London, UK
Email: a.steptoe@ucl.ac.uk

3rd author: Li-Jung Chen*, PhD
Department of Exercise Health Science, National Taiwan University of Sport, Taichung, Taiwan
Department of Epidemiology and Public Health, University College London, London, UK
Address: No. 271, Lixing Road, Taichung City, Taiwan 404
E-mail: ljchen@ntupes.edu.tw; Telephone: +886 (4) 2221-3135 ext.1310

*: Corresponding author

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Abstract

Purpose: Exercise is associated with reduced risk of depressive symptoms at older ages, while recent work suggests that the apolipoprotein E type 4 allele (APOE-e4) may increase risk. There are no studies of whether APOE-e4 moderates the relationship between exercise and later life depressive symptoms. This study aimed to explore whether the prospective associations between exercise and subsequent depressive symptoms were distinct between APOE-e4 carriers and non-carriers using nationwide data.

Methods: Data from 639 participants (mean age= 66.14, SD= 7.26) in 2000 with 6 years of follow-up were studied. Depressive symptoms were assessed using the Center for Epidemiologic Studies–Depression Scale. Exercise and the APOE genotype were also assessed at baseline. Negative binomial regression models were conducted to examine the combined effects of exercise and APOE-e4 status on subsequent depressive symptoms when controlling for baseline depressive symptoms and other covariates. Sensitivity analyses to test for confounding, reverse causality, and attrition were conducted.

Results: Among APOE-e4 carriers, there was no significant difference in depressive symptoms between high active and low active groups. In contrast, high active APOE-e4 non-carriers had fewer depressive symptoms than low active APOE-e4 non-carriers. The beneficial effect of exercise on depressive symptoms is restricted to APOE-e4 non-carriers. Sensitivity analyses provided further support for the robustness of these findings.

Conclusions: This is the first prospective study investigating whether APOE-e4 moderates the association between exercise and depressive symptoms. It proposes that genetic variation in APOE may influence the effect of exercise on

depressive symptoms**.**

Keywords: Physical activity, depression, mental health, aging, moderation

Prospective associations of exercise and depressive symptoms in older adults:

The role of apolipoprotein E4

Introduction

Depressive disorders, including major depression and dysthymia, have been identified as the leading causes of global disease burden measured in years lived with disability (YLDs) and disability adjusted life years (DALYs) for more than two decades [1]. Depression is also projected to become the single highest contributor to the global disease burden by 2030, above heart disease, stroke, HIV/AIDS and diabetes [2]. Depressive symptoms are commonly associated with higher rates of morbidity and mortality and have major implications for deterioration in physical, cognitive and social functioning [3]. The prevalence of depressive symptoms in community-dwelling older adults ranges between 8% and 16% [4]. Given this increasing societal and economic impact [5], identifying modifiable and non-modifiable factors that can prevent or mitigate depressive symptoms in aging populations is important for public health and health care systems.

Physical activity is a modifiable lifestyle factor that is central to successful aging [6; 7]. There are well-documented benefits of physical activity for a range of physical and mental conditions, and these positive health effects are sustained at older ages [8-10]. According to recent systematic reviews and meta-analyses, the association of physical activity with depression/depressive symptoms in older adults is relatively consistent, with an inverse relationship in cohort studies [11], and a reduction of symptom severity in randomized controlled trials [12; 13]. Additionally, a recent randomized trial demonstrated that exercise may be also a safe and efficacious augmentation to

antidepressant treatment in late-life major depression [14].

The apolipoprotein E type 4 allele (APOE-e4) genotype is a known risk factor of Alzheimer's disease and cognitive impairment [15; 16] and it has been suggested that it modifies the association between physical activity and cognitive decline [17; 18]. The evidence for a relationship between APOE-e4 and depression is more equivocal, with studies showing both positive and null results. The variation in results may be due to methodological limitations such as a small or non-representative samples, a short period of follow-up, low response rates and failing to exclude the cases of prodromal dementia [19]. A recent large population-based study based on rigorous methodology has provided evidence that APOE-e4 is prospectively associated with a higher risk of depressive symptoms in later life [20].

It is not known whether there is a role for APOE-e4 genotype in modulating the effect of physical activity on depressive symptoms at older ages. To fill the gap in literature, this study aimed to explore whether the prospective associations between physical activity and subsequent depressive symptoms differed between APOE-e4 carriers and non-carriers in a six-year follow-up of a population-based sample of middle-aged and older adults. We also adjusted for multiple potentially confounding factors, and carried out sensitivity analyses to test for confounding, reverse causality, and attrition.

Methods

Study design and sample

This was a prospective cohort study based on the two-wave data from the Social Environment and Biomarkers of

Aging Study (SEBAS) in 2000 and 2006, which was a nationally representative longitudinal survey. The SEBAS surveys were conducted by Taiwan Department of Health and Taiwan Provincial Government in collaboration with Georgetown University and Princeton University in US. In 2000, the total sample of 1,023 participants aged 54 or older were interviewed face-to-face at home and then attended a hospital-based physical examination several weeks later. Among them, 757 participants were interviewed (response rate= 89.5%, the 177 deceased cases were excluded from denominator of response rate) at the second wave of SEBAS. Approximate 85% of those interviewed (three of them died before the physical examination) then completed the hospital-based physical examination. These individuals (n= 639) constituted the data set for these analyses. The sampling strategy and data collection procedures of the SEBAS have been reported in more detail elsewhere [21]. This study obtained ethics approval from Antai Medical Care Cooperation Antai- Tian-Sheng Memorial Hospital Institutional Review Board, Taiwan (reference number: TSMHIRB 15-078-CO).

Measures

Outcome variables: Depressive symptoms

A ten-item Chinese version of the Center for Epidemiologic Studies–Depression Scale (CES-D) was used to assess depressive symptoms with a potential range of 0 to 30. This scale has demonstrated adequate factorial and criterion validity [22] and has also been shown to be an appropriate instrument for measuring depressive symptoms in cross-cultural studies [23; 24]. The Cronbach's alpha reliability coefficients for the 10-item CES-D ranged between 0.84 and 0.86 in Taiwan Longitudinal Study of Aging [25].

Exposure variable: Exercise

Exercise as a subcategory of physical activity is planned, repetitive and purposeful attempt to improve fitness and health. It may comprise leisure activities such as brisk walking, swimming, dancing, tai-chi, and competitive sports. At baseline, participants were asked 'Did you usually engage in physical exercise?' with four response categories being provided (none, 1-2, 3-5, and 6+ sessions per week). Reliability and validity of this measure has been demonstrated in a previous study [26]. Among 96 community-dwelling older adults in Taiwan, test–retest reliability with a 3-day interval was r = 0.65 ($p< 0.001$), which is close to the conventional level (0.70). Spearman's correlation was utilized to examine the concurrent validity between self-reported exercise frequency and triaxial accelerometer measures (ActiGraph GT3X), including one-week energy expenditure ($\rho= 0.36$, $p< 0.001$) and walking steps ($\rho= 0.41$, $p< 0.001$) [26]. The reliability and validity of this measure are comparable to those in previous studies using self-reported physical activity questionnaires in aged populations [27; 28].

Covariates

The following potentially relevant factors in 2000 SEBAS (baseline) were included as covariates based on previous studies [11; 29]: (i) socio-demographic factors: sex, age (54-64, 65-74, 75+), education level (no formal schooling, primary school, secondary school+), marital status (married/cohabitating, others); (ii) lifestyle behaviors: current alcohol consumer (yes vs. no), and current smoker (yes vs. no); (iii) health status: APOE genotypes were assessed by blood specimen using the polymerase chain reaction amplification refractory mutation system (PCRARMS) and polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) techniques [30].

The genotypes were groups as APOE-e4 carrier and APOE-e4 non-carrier; body mass index (BMI) (<18.50, 18.50-23.99, 24-26.99, 27+) [31]; Charlson comorbidity index: (none=0; mild= 1; severe= 2+), which considers the number and severity of chronic diseases, including hypertension, heart disease, stroke, diabetes, cancer, chronic obstructive pulmonary disease (COPD), liver or gall bladder disease, renal disease, gastric ulcer/stomach ailment, and arthritis [32; 33]; difficulties in activities of daily living (no difficulties at all vs. some or great difficulties); and cognitive impairment assessed using the Short Portable Mental Status Questionnaire (SPMSQ) in which higher scores represent poor cognitive performance [34].

Data analysis

Descriptive statistics for depressive symptoms were calculated first to characterize the sample structure. Mann Whitney U test and Kruskal-Wallis test were used to test for difference across levels of exercise and covariates due to the violation of normality. Variables with a p value < 0.25 were included in the regression models as covariates. Exercise frequency was categorized into three levels in univariate analysis (0-2, 3-5, 6+ sessions/ week). However, the number of participants with three to five sessions per week was relatively small, and older adults engaging in exercise less than 6 sessions per week were more likely to have higher levels of subsequent depressive symptoms. Therefore, exercise frequency was classified into two levels in the following multivariable analyses (0-5 [low active] vs. 6+ [high active] sessions/ week); this threshold is consistent with the international guidelines to be active every day in as many ways as you can, with physical activity on five or more times per week [35].

Data were analyzed using negative binomial regression models given that the outcome variable was an over-dispersed count with a highly skewed distribution. Although a zero-inflated negative binomial model may fit a little better than the conventional negative binomial model, it made little difference to the results [36]. For the sake of simplicity, we utilized conventional negative binomial regression in this study. The regression models were conducted to examine the prospective associations between exercise and future depressive symptoms when controlling for baseline depression, socio-demographic variables, lifestyles behaviors, and health status. The regression coefficients (B) are not directly interpretable in this method due to the nonlinearity of the negative binomial distribution. Thus, the incident rate ratios (RRs) (e^B) are computed. For instance, if the RR for scores of depressive symptoms by exercise levels (low active vs. high active) is 1.50, the average score of depressive symptoms among participants with the low active level of exercise is 1.50 times higher than those with high active level.

The independent effects of exercise levels (low active vs. high active) and APOE-e4 status (carrier vs. non-carrier) on depressive symptoms were assessed in Model 1. To examine whether APOE-e4 moderates the association of exercise with future depressive symptoms, groups involving the presence or absence of APOE-e4 and exercise (high active vs. low active) were then created: low active APOE-e4 carrier, high active APOE-e4 carrier, low active APOE-e4 non-carrier, high active APOE-e4 non-carrier. This variable was included in the multivariable adjusted regression model for assessing the combined effects of the two variables on subsequent depressive symptoms in Model 2. To assess the interaction between levels of exercise and APOE-e4 carrier status, the Model 2 was rerun by further including an interaction term in the model.

Several sensitivity analyses were performed to address confounding, reverse causation, and attrition. First, to take account of the possibility that individuals with chronic physical illnesses would be both depressed and inactive, participants who had chronic obstructive pulmonary diseases (n=52), arthritis (n=120), difficulty with activities of daily living (n=17), and or all three conditions (n=149) at baseline were excluded in Models 3 - 6. Then, to reduce the potential impact of cognitive deterioration on depressive symptoms at baseline, participants with cognitive impairment (Scores of the SPMSQ $\geqq$ 3, n=30) were excluded Model 7 [37]. Finally, to assess the influence of the sample attrition, the Model 2 was repeated after conducting multiple imputation (Model 8).

Data analyses were completed in 2016. All analyses were conducted using IBM SPSS 20.0 software and a p value < 0.05 was considered statistically significant.

Results

The differences in depressive symptoms in 2006 grouped by baseline characteristics are shown in Table 1. It can be seen that depressive symptoms at baseline correlated strongly with symptoms 6 years later ($\rho = 0.34$, $p<0.001$). Additionally, most other variables, with the exception of smoking, alcohol consumption and BMI, were significantly associated with depressive symptoms on follow-up ($p<0.05$). Participants who were female, older, with a lower level of educational attainment, divorced/separated or widowed, fewer sessions of exercise, and who were APOE-e4 carriers, and had mild or severe comorbidities or cognitive impairment and experienced difficulty in activities of daily living, were more likely to have higher levels of depressive symptoms at follow-up (Table 1).

Table 1 here

The multivariable adjusted model showed that low active participants (rate ratio [RR] = 1.24 (95% CI= 1.03-1.49, reference: high active) and APOE-e4 carriers (RR= 1.38 (95% CI= 1.08-1.75, reference = APOE-e4 non-carriers)) both had higher risks of subsequent depressive symptoms (Model 1, Table 2). Compared with high active APOE-e4 non-carriers, low active APOE-e4 carriers had a RR of 1.57 (95% CI= 1.12-2.18) for depressive symptoms, high active APOE-e4 carriers had a RR of 1.66 (95% CI= 1.14-2.42), and low active APOE-e4 non-carriers had a RR of 1.31 (95% CI= 1.06-1.60) (Model 2). The interaction between APOE-e4 carrier status and exercise was also significant (p= 0.046).

Table 2 here

This interaction is illustrated in Figure 1 which presents the multivariable adjusted means of depressive symptoms in 2006 stratified by exercise and APOE-e4 status in 2000. Overall, it shows that APOE-e4 carriers had elevated levels of depressive symptoms than those in non-carriers. Among APOE-e4 carriers, there was no significant difference in

depressive symptoms between high and low exercise groups. In contrast, APOE-e4 non-carriers who were highly active had fewer depressive symptoms than those who were less active. The high active APOE-e4 non-carriers had the lowest levels of depressive symptoms among the four groups, adjusted for covariates including baseline depressive symptoms.

Figure 1 here

The sensitivity analyses are detailed in Table 3. In Models 3 - 5, participants with COPD, arthritis, and ADL difficulty were excluded respectively, and the results were similar to the full sample (Model 2 in Table 2). In model 6, the combination of all these exclusions reduced the sample size quite markedly, but the association patterns did not alter much. The additional sensitivity analysis excluding participants with cognitive impairment at baseline (Model 7) yielded similar results. Finally, after imputation, the Model 8 also demonstrated the similar association patterns although the associations of strength were slightly attenuated. In each case, greater exercise was associated with fewer depressive symptoms on follow-up among non-carriers, but not in APOE-e4 carriers.

Table 3 here

Discussion

This population-based six-year follow-up study revealed that older adults who engaged in exercise more frequently or did not carry the APOE-e4 genotype had relatively few subsequent depressive symptoms. However, the protective effect of exercise differed between APOE-e4 carriers and non-carriers. There was no significant difference in depressive symptoms between high and low active APOE-e4 carriers. In contrast, there was a protective effect of exercise on depressive symptoms among APOE-e4 non-carriers. Of the four groups, high active APOE-e4 non-carriers had the lowest level of depressive symptoms. These results were observed in negative binomial regression models after adjusting for baseline depressive symptoms, socio-demographic variables, lifestyle behaviors, and comorbid conditions. Sensitivity analyses for assessing confounding, reverse causation, and attrition provided further support for the robustness of these findings.

The etiology of depression is multi-factorial and remains equivocal. Therefore, it is probable that no single mechanism accounts for the effects of exercise on depression. It is likely that the interaction of several involving hormones, neurotrophic factors, systemic inflammation, oxidative stress and cortical plasticity and activity, may explain the antidepressant effects of exercise [38]. To our knowledge, this work is the first prospective study investigating whether APOE-e4 moderates the association between exercise and depressive symptoms. Although there is a growing body of evidence that physical activity can mitigate the risk of depressive symptoms in older adults [11],

this study suggests that the effect of physical activity is restricted to non-carriers of the APOE-e4. Our study also confirms the association between APOE-e4 and future depressive symptoms described in a large cohort of Swedish men and women aged 70-92 years [20]. The mechanism by which APOE-e4 moderates the relationships between exercise and depressive symptoms warrants further research. One explanation may be that APOE-e4 is associated with brain atrophy, which has been identified as a risk factor of depression in later life. [20; 39] In addition, APOE-e4 is related to a higher risk of cardiovascular disease [40], cerebrovascular disease [41], metabolic syndrome and diabetes [42], which could also increase the risk of depressive symptoms [43; 44]. It should, however, be pointed out that the presence of high blood pressure, heart disease, diabetes, and stroke at baseline was taken into account in our analyses through the Charlson index of comorbidity. Given the potential effects of these intermediate factors, it is possible that exercise may simply not be a strong predictor of depressive symptoms among APOE-e4 carriers with advancing age.

The moderating effect of APOE-e4 on the exercise - depressive symptom relationship was further confirmed using sensitivity analyses. Conditions such as chronic obstructive pulmonary diseases, arthritis, and difficulty with activities of daily living may have affected exercise status at baseline [26] while also being associated with a higher risk of subsequent depressive symptoms [29]. After excluding participants with these conditions, the results remained similar to those based on the full sample. Similarly, depressive symptoms may be a prodromal feature of dementia [45], so participants with cognitive impairment were excluded to reduce the potential influence of cognitive deterioration at baseline on subsequent depressive symptoms (Model 7). Again, the patterns between APOE-e4 status and physical activity persisted. These analyses provide further evidence that the moderating role of APOE-e4 on the

relationship between exercise and depressive symptoms in older adults is not secondary to confounding factors.

Although this study was conducted adjusting for a comprehensive range of potential confounders based on a nationwide population-based sample with a six-year follow-up period, it inevitably has some limitations. First, the assessment of exercise was based on self-reported assessment, which may have been susceptible to recall bias. Self-report measures of physical activity of older adults with cognitive impairment may be compromised; however, the additional sensitivity analysis excluding participants with cognitive impairment at baseline demonstrated the robustness of the findings. Second, the sample attrition rate was high, which may be due to the high mortality in this aging population. Although there were no significant differences between individuals who did and did not engage in the 2006 survey in terms of sex, exercise levels and the presence of APOE-e4, those who did not attend the second survey tended to be older, had lower education attainment, and experienced more chronic disease and depressive symptoms at baseline (p for χ^2 test < 0.05) (data not shown). However, the sensitivity analysis using multiple imputation provided further support for the accuracy of the findings. Third, this research was based on two waves of data collection, and this limited our ability to identify the onset date of depression episodes and examine the effect of changes in exercise on subsequent depressive symptoms. Additionally, this study aimed to assess factors relevant to the association between exercise and depressive symptoms rather than clinical significance of depression. The findings should be interpreted with caution. Finally, this is an observational study, which cannot establish causal relationships. A well-designed randomized controlled trial with a representative sample would be needed to verify these findings.

In conclusion, APOE-e4 is a significant risk factor for depressive symptoms at older ages. This study revealed

that the relationship between exercise and depressive symptoms may differ between APOE-e4 carriers and non-carriers. The effect of exercise on subsequent depressive symptoms is restricted to APOE-e4 non-carriers. This has implications for mental health promotion. However, since this is first longitudinal population-based study documenting such an association, more studies are required to verify the findings.

Compliance with Ethical Standards

a. Funding: This work was supported by Taiwan Ministry of Science and Technology (105-2628-H-018-001-MY2).

b. Disclosure of potential conflicts of interest: None.

c. Ethical approval: Ethics approval for this study was obtained from Antai Medical Care Cooperation Antai-Tian-Sheng Memorial Hospital Institutional Review Board, Taiwan (reference number: TSMHIRB 15-078-CO). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

d. Informed consent: A signed, informed consent form was provided by each participant before conducting the study.

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