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Research paper

Associations of healthy lifestyle with depression and post-depression dementia: A prospective cohort study

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ABSTRACT

Background: Depressive symptoms may be a risk factor or prodrome of dementia, but the modifiable risk factors for dementia after onset of depression has not been fully elucidated. The current study aimed to investigate the associations of lifestyle factors with depression and post-depression dementia.

Methods: Our analysis was based on data from the ongoing UK Biobank study, which included 497,533 participants (age 37–73 years) between 2006 and 2010, and thereafter followed up to 2020. High-risk lifestyle factors included current smoking, heavy alcohol intaking, poor diet pattern, physically inactive. Multistate models were used to estimate the transition-specific hazard ratios (HRs) and 95 % confidence intervals (CIs).

Results: During a 14.8-year follow-up, 23,164 participants developed depression, and 989 developed post-depression dementia. The incidence rate of dementia in people with depression was far more than those who were free of depression. In multistate model, high-risk lifestyle factors were substantially associated with higher risks of incident depression (HR = 2.14, 95 % CI: 1.95–2.35), dementia (HR = 1.87, 95 % CI: 1.51–2.31), and post-depression dementia (HR = 1.72, 95 % CI: 1.13–2.62). When the analyses were divided by individual lifestyle factors, we found that only physically inactive contributed significantly to the development of dementia after the onset of depression (HR = 1.15, 95 % CI: 1.01–1.30).

Conclusion: Our study found that high-risk lifestyle factors were associated with higher risk of transition from depression to dementia, highlighting the great significance of integrating comprehensive behavioral interventions, particularly for regular physical activity, for prevention of both depression and post-depression dementia.

1. Introduction

Depression and dementia are the most common neuropsychiatric syndromes in the elderly. According to estimates of the World Health Organization, over 300 million people suffered from depression in 2015, equivalent to 4.4 % of the world's population, and depression has become the leading cause of global disease burden (WHO, 2017). There were 47.5 million people diagnosed with dementia worldwide in 2016, it is expected to affect >135.5 million individuals in 2050 (Beard et al., 2016). Depression and dementia commonly coexist, but how depression developed dementia has not been well established. Several meta-analyses suggested that chronic depression during life may be etiologically associated with an increased risk for developing dementia (Diniz et al., 2013; Ownby et al., 2006), whereas another view is that depression occurring for the first time in late life may reflect a prodromal stage of dementia (Barnes et al., 2012; Brommelhoff et al., 2009; Li et al., 2011). There is evidence that both depression and dementia showed similar neurobiological changes, indicating shared risk factors, such as lifestyle factors (Bennett and Thomas, 2014). Whether depression is a causal risk factor for dementia or a prodromal state, it has important implications for public health and clinical practice if lifestyle modification can reduce the risk of dementia among individuals with depression.

Our previous studies have reported that healthy lifestyle was associated with lower risk of depression (Cao et al., 2021). In addition, there is also a wide of evidence elucidating an association between healthy lifestyle and dementia (Dhana et al., 2020; Licher et al., 2019; Lourida et al., 2019). However, such fragmented analyses by only focusing on

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one stage of disease progression makes it challenging to compare the impact of lifestyle factors on risk of dementia before or after onset of depression. Moreover, it is unclear whether and to what extent high-risk lifestyle factors accelerate the development of dementia after onset of depression using a longitudinal sample, initially free from depression and dementia. Multistate model could be used to assess the risk factors that adversely affect temporal progression from a healthy state to depression and subsequent comorbid dementia. The identification of such factors, particularly potentially modifiable lifestyle factors, would be of public health significance for releasing or delaying the progression of dementia in people with depression.

In the current study, therefore, we used multistate model to examine the potentially different effect of combined and individual high-risk lifestyle factors on transition from healthy status to depression, and subsequent progression to dementia.

2. Methods

2.1. Study design and population

This was a prospective, population-based cohort study of participants enrolled in the UK Biobank cohort. Between April 2006 and December 2010, the UK Biobank recruited 502,528 adults (37–73 years old) from the general population. Participants attended one of 22 assessment centers across England, Scotland, and Wales, where they completed nurse-led electronic questionnaires, physical examination, and biological samples collections (Sudlow et al., 2015). Participants were excluded if they had history of depression ($n = 4757$) and dementia ($n = 238$) before recruitment, leaving 497,533 participants included in final analyses. All participants gave written informed consent prior data collection.UK Biobank has full ethical approval from the NHS National Research Ethics Service (16/NW/0274).

2.2. Assessment of high-risk lifestyle factors

In the current study, Lifestyle factors included tobacco smoking, alcohol intaking, physical activity, and healthy diet pattern, which were assessed at baseline using a touchscreen questionnaire. Smoking status was categorized as current or no current smoking. Regular physical activity was defined as meeting the American Heart Association recommendations of at least 150 min of moderate activity per week or 75 min of vigorous activity per week (or an equivalent combination) (Lloyd-Jones et al., 2010). A healthy diet was defined in UK Biobank as an adequate intake of at least 4 of 7 dietary components (fruits, vegetables, whole grains, refined grains, fish, unprocessed meat, and processed meat), following the recommendations on dietary components for cardiovascular health (Mozaffarian, 2016). Moderate consumption of alcohol was defined as 0 to 14 g/d for women and 0 to 28 g/d for men, with the maximum limit reflecting U.S. dietary guidelines (Services, 2020). For each healthy lifestyle factor, participants received a score of 1 if they met the criterion and 0 if they did not. The sum of these 4 components yielded a final score ranging from 0 to 4, with higher scores indicating a healthier lifestyle. Details on the assessment of individual lifestyle factors can be found in Appendix 1.

2.3. Ascertainment of depression and dementia

Incident cases of interest (including depression and dementia) were identified through linkages to Hospital Episode Statistics (HES). All residents in England, Scotland, and Wales have a unique National Health Service (NHS) identification number. Incident cases of all-cause death were identified through linking to national death registries. All events were coded according to the International Classification of Diseases, 10th Revision. In the present analysis, depression was defined by code F31.3, F31.4, F31.5, F32, F33, dementia was defined by F00-F03, G30-G31. Participants were followed starting at inclusion until the incidence of depression or dementia, or ending of the study (December 31, 2020).

2.4. Covariate assessment

All analyses in our study were adjusted for age, sex, ethnicity, Townsend deprivation index, body mass index (BMI), hypertension, hyperglycemia and hypercholesterolemia. Information on participants' age, sex and ethnicity was collected using a self-reported questionnaire at baseline. The Townsend deprivation index was assigned as a continuous measure based on postcodes, which were derived from census data on housing, employment, social class, and car availability; a higher index indicated more deprivation (Townsend PPP, 1988). We calculated BMI as weight (in kilograms) divided by height (in meters) squared. Hypertension was defined as systolic blood pressure $\geq$ 140 and/or diastolic blood pressure $\geq$ 90 mmHg and/or use of antihypertensive medication. Hypercholesterolemia was defined as total cholesterol $\geq$ 5 mmol/L or use of lipid-lowering medication. Hyperglycemia was defined as fasting blood glucose $\geq$ 7.0 mmol/L, HbA1c $\geq$ 6.5 or use of antidiabetic medications. UK Biobank genotyping was conducted by Affymetrix using a bespoke BiLEVE Axiom array and the Affymetrix UK Biobank.

2.5. Statistical analysis

We summarized baseline characteristics by incidence of depression and dementia using descriptive statistics, reporting the mean and standard deviation (SD) of continuous variables, and proportions for categorical variables.

Multistate Markov models were applied to examine the role of combined and individual lifestyle factors in the temporal progression from healthy status to the development of depression and subsequent onset of comorbid dementia (Fig. 1). Multistate models (Putter et al., 2007), an extension of competing risk survival analysis, could simultaneously estimate the risks of different transitions from an initial state to intermediate events and subsequently to final states in the same framework. Such an analytical approach could clearly delineate the time sequence and deal with competing risks in disease progress. These models are Markov processes, and the estimated probability of going to a future state only depends on the current state and not on history. Each transition was modeled using Cox proportional hazards models. Results are presented as transition-specific HRs and 95 % CIs for depression onset and subsequent dementia. The linear trend test was performed by assigning the number of high-risk lifestyle factors as continuous variables in a separate model. Missing data on variables were imputed by the multiple imputation method with chained equations for 5 imputations to reserve all complete case and reduce the potential for inferential bias.

Moreover, Cox proportional hazards models were used to examine the longitudinal associations between lifestyle factors and dementia among individuals with prevalent depression at baseline. Prevalent depression was measured at baseline using the Patient Health Questionnaire (PHQ)-2 (depression items) (Kroenke et al., 2003) and linked HES.

We also carried out other several sensitivity analyses to ensure the robustness of the results. First, each status in multistate model faced a risk of death, particularly suicide events in depression patients. Therefore, death was included as a compete event to test the association of post-depression with incident dementia. Second, a lagged-time analysis in multistate model that excluding those who developed dementia within one year after the onset of depression was conducted because depression that occurs shortly before dementia onset can be a prodrome of dementia (Bennett and Thomas, 2014). Third, we excluded individuals with prevalent coronary heart disease, stroke and cancer because lifestyle could be influenced by major chronic diseases.

All analyses were performed using STATA 15 statistical software (StataCorp) and R i386 3.4.3 (R Foundation for Statistical Computing). All P values were two-sided, and $P < 0.05$ was considered statistically

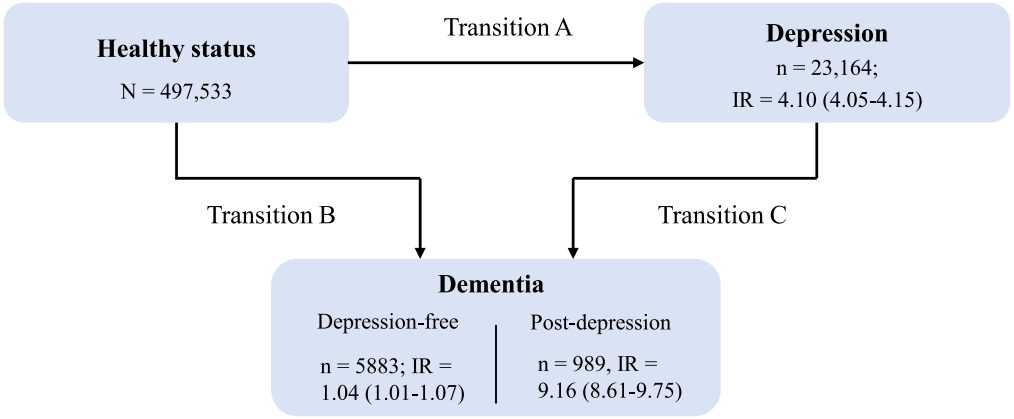

Fig. 1. Schematic representation of multistate model.
Depression-free dementia indicated those occurred without experiencing depression. Post-depression indicated those occurred dementia after onset of depression. IR, incidence rate per 1000 person-years.

significant.

3. Results

Of the 497,533 participants included in this study, the mean (SD) age was 56.5 (8.1) years and the proportion of women was 54.4 %. Table 1 shows the participants' characteristics by developing depression and dementia at the end of follow-up. During a maximum follow-up of 14.8 years, a total of 23,516 (4.7 %) individuals had developing depression, 6872 (1.4 %) dementia, of which included 5883 depression-free dementia and 989 post-depression dementia.

Table 1
Characteristics of the study population as a function of depression, dementia and comorbidity at the end of follow-up.

Characteristics	Total (N)	Depression		Dementia	
		No	Yes	No	Yes
Age, mean (SD)	497,533	56.5 (8.1)	56.6 (8.1)	56.4 (8.1)	63.9 (5.2)
Women, sex	270,469	255,405 (53.9)	15,064 (64.1)	267,341 (54.5)	3128 (45.5)
Ethnicity					
White	470,370	447,985 (94.5)	22,385 (95.2)	463,797 (94.5)	6573 (95.6)
Black	8369	8060 (1.7)	309 (1.3)	8249 (1.7)	120 (1.7)
South Asian	11,380	10,958 (2.3)	422 (1.8)	11,270 (2.3)	110 (1.6)
Mixed background	7414	7014 (1.5)	400 (1.7)	7345 (1.5)	69 (1.0)
Educational attainment					
College or above	161,710	156,157 (32.9)	5553 (23.6)	160,327 (32.7)	1383 (20.1)
Professional qualifications	251,157	238,854 (50.4)	12,303 (52.3)	248,060 (50.6)	3097 (45.1)
None above	84,666	79,006 (16.7)	5660 (24.1)	82,274 (16.8)	2392 (34.8)
Townsend deprivation index	497,533	−1.35 (3.1)	−0.52 (3.4)	−1.32 (3.1)	−0.83 (3.3)
Physical inactive	228,371	215,934 (45.5)	12,437 (52.9)	224,969 (45.8)	3402 (49.5)
Current smoking	51,846	47,611 (10.0)	4235 (18.0)	51,052 (10.4)	794 (11.6)
Poor diet	258,339	245,397 (51.8)	12,942 (55.0)	255,126 (52.0)	3213 (46.7)
Heavy alcohol intake	151,826	145,537 (30.7)	6289 (26.7)	149,981 (30.6)	1845 (26.8)
BMI, kg/m^2, mean (SD)	497,533	27.4 (4.7)	28.8 (5.7)	27.4 (4.8)	27.8 (4.9)
Hypertension	269,596	256,530 (54.1)	13,066 (55.6)	264,510 (53.9)	5086 (74.0)
Hyperglycemia	462,356	441,335 (93.1)	21,021 (89.4)	33,983 (6.9)	1194 (17.4)
Hypercholesterolemia	417,495	397,498 (83.9)	19,997 (85.0)	411,493 (83.9)	6002 (87.3)

Data are n (%), unless otherwise specified. BMI, body mass index; SD, standard deviation.

Multistate analyses distinguished the roles of high-risk lifestyle factors in the temporal transitions from healthy status to the development of depression and subsequently to dementia (Fig. 1). The incidence of dementia in people with depression was far more than those who were free of depression (9.16 [95 % CI: 8.61–9.75] vs. 1.04 [95 % CI: 1.01–1.07] per 1000 person-years). In the multistate model (Table 2), 4 high-risk lifestyle factors were associated with a 2.14 (95 % CI: 1.95–2.35) times higher risk of depression compared to those with 0 high-risk lifestyle factor. High-risk lifestyle factor was also significantly associated with an increased risk of incident dementia in those with depression (HR = 1.72, 95 % CI: 1.13–2.62), and those free of depression (HR = 1.87, 95 % CI: 1.51–2.31). These results were primarily consistent to sex subgroup (Appendix 2).

Then, we used multistate model to examine the role of individual lifestyle factors in the transition from healthy status to depression, and subsequent onset of dementia, which revealed that only physically inactive contributed to the development of dementia after the onset of depression (HR = 1.15, 95 % CI: 1.01–1.30) (Fig. 2). In addition, among the individuals with prevalent depression at baseline, we found high-risk lifestyle factors were also associated with higher risk of dementia among the population (5 vs. 0 lifestyle factor: multivariable-adjusted HR = 2.50, 95 % CI: 1.60–3.93) (Table 3).

The consistent results were also observed by several sensitivity analyses if we took death as a compete event in each status of the transition (Appendix 3); excluded those with <1 year of follow-up in the transition from depression to dementia in multistate model (Appendix 4); excluded those with prevalent cancer or cardiovascular disease at baseline (Appendix 5).

4. Discussion

In this large-scale cohort of nearly half a million participants from UK Biobank, we found that 1) The incidence rate of dementia in people with depression was far more than those free of depression; 2) High-risk lifestyle factors were associated with higher risk of depression and post-depression dementia; 3) Among individual high-risk lifestyle factors, only physically inactive was associated with higher risk of dementia after the onset of depression. Our findings highlight the need to adherence to a healthy lifestyle, particularly for physically active, for the prevention of both depression and post-depression dementia.

Table 2
The hazard ratios for transition from healthy status to depression and subsequent dementia by high-risk lifestyle factors.

Transitions	Number of high-risk lifestyle factors					*P* for trend[c]
	0	1	2	3	4	
A: Healthy to depression						
Model 1[a]	1 (Ref.)	1.15 (1.10–1.20)	1.37 (1.31–1.43)	1.79 (1.70–1.88)	2.40 (2.19–2.64)	<0.001
Model 2[b]	1 (Ref.)	1.11 (1.06–1.15)	1.26 (1.21–1.31)	1.61 (1.53–1.69)	2.14 (1.95–2.35)	<0.001
B: Healthy to dementia						
Model 1[a]	1 (Ref.)	1.07 (1.00–1.15)	1.10 (1.02–1.18)	1.24 (1.12–1.38)	2.13 (1.73–2.63)	<0.001
Model 2[b]	1 (Ref.)	1.05 (0.98–1.13)	1.06 (0.98–1.14)	1.17 (1.05–1.30)	1.87 (1.51–2.31)	<0.001
C: Depression to dementia						
Model 1[a]	1 (Ref.)	1.09 (0.91–1.31)	0.96 (0.79–1.16)	1.12 (0.88–1.42)	1.85 (1.22–2.80)	0.338
Model 2[b]	1 (Ref.)	1.08 (0.90–1.30)	0.94 (0.78–1.15)	1.08 (0.85–1.37)	1.72 (1.13–2.62)	0.507

[a] Model 1 was adjusted for age and sex.
[b] Model 2 was additionally adjusted for ethnicity, Townsend deprivation index, BMI, hypertension, hyperglycemia and hypercholesterolemia.
[c] The linear trend test was performed by using number of high-risk lifestyle factors as a continuous variable in a separate model.

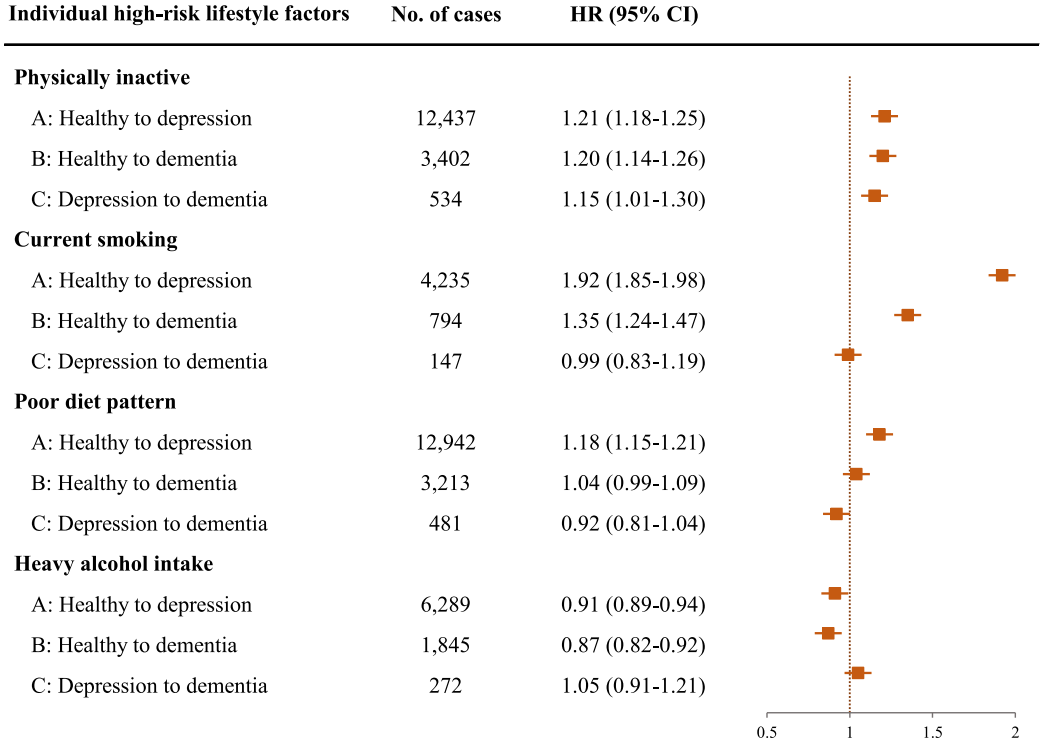

Fig. 2. The hazard ratios for transition from healthy status to depression and subsequent dementia by individual high-risk lifestyle factors.
Multistate models were used to examine the roles of four lifestyle factors in the transition from healthy status to depression and then to dementia. The models were adjusted for age, sex, ethnicity, Townsend deprivation index, body mass index, hypertension, hyperglycemia and hypercholesterolemia. Physically inactive was defined as not meeting the American Heart Association recommendations of at least 150 min of moderate activity per week or 75 min of vigorous activity per week (or an equivalent combination). Poor diet pattern was defined as an adequate intake of <4 of 7 dietary components (fruits, vegetables, whole grains, refined grains, fish, unprocessed meat, and processed meat). Heavy alcohol intake was defined as >14 g/d for women and >28 g/d for men.

Our primary objective was to explore the risk of transition from depression to dementia using multistate models. Our approach is an essential supplement for mediation model, in which the goal is to estimate whether depression may explain the association between lifestyle factors and incidence of dementia. In addition, we provided the further evidence regarding how high-risk lifestyle factors could affect the onset and prognosis of depression. On the one hand, results from our study suggested detrimental roles of high-risk lifestyle factors in the transition from a healthy state to depression, a healthy state to dementia and depression to dementia. On the other hand, multistate models also showed that high-risk lifestyle factors were associated with increased risk of dementia regardless of the presence of depression during the follow-up.

The relationship between depression and dementia is complex and still not well understood. A few different views exist regarding how the two disorders are related as well as the underlying neurobiological mechanisms at work. On the one hand, most previous evidence showed that depressive symptoms may represent a prodrome of dementia. In a 28-year follow-up cohort study, depressive symptoms later in life were significantly associated with risk of incident dementia, whereas depressive symptoms earlier in the study were not (Singh-Manoux et al., 2017). On the other hand, there is convincing evidence to support both the notion that early life depression but not late-onset depression can act as a risk factor for later life dementia (Geerlings et al., 2008; Pálsson et al., 1999). Evidence also supported an relationship between depression symptoms and dementia, even when depression symptoms occurred >25 years before onset of dementia, implying that depression is a risk factor for incidence of dementia (Heser et al., 2013). Together, a prior narrative review has concluded convincing evidence to support both early-life depression being a risk factor of dementia, and late-life depression being a prodrome of dementia (Bennett and Thomas, 2014). In our view, whether depression is a risk factor or a prodrome of dementia, the occurrence interval between depression and dementia is relatively longer. Therefore, we hypothesized that the risk of post-

Table 3
The associations of high-risk lifestyle factors with dementia among individuals with prevalent depression at baseline.

Number of high-risk lifestyle factors	Cases	HR (95 % CI)	
		Model 1[a]	Model 2[b]
0	83		
1	201	1.07 (0.83–1.38)	1.03 (0.80–1.34)
2	217	1.32 (1.02–1.71)	1.24 (0.96–1.60)
3	74	1.27 (0.92–1.74)	1.14 (0.83–1.57)
4	26	2.78 (1.78–4.34)	2.50 (1.60–3.93)
Per 1 increment		1.17 (1.08–1.27)	1.13 (1.04–1.23)
P for trend[c]		<0.001	0.003

[a] Model 1 was adjusted for age and sex.
[b] Model 2 was additionally adjusted for ethnicity, Townsend deprivation index, body mass index, hypertension, hyperglycemia and hypercholesterolemia.
[c] The linear trend test was performed by using number of high-risk lifestyle factors as a continuous variable in a separate model.

depression dementia would be reduced if we capture the strategy of lifestyle modification during the time.

Our results bolster the notion that high-risk lifestyle factors offer an approach to dementia prevention, even in those developed depression. A recent study that included 2 longitudinal cohort suggested that a healthy lifestyle was associated with a substantially lower risk of incident Alzheimer's dementia in general population (Dhana et al., 2020). Two exposure-genetic studies also found that unfavorable lifestyle increased the risk of long-term risk of dementia, independently of genetic risk (Licher et al., 2019; Lourida et al., 2019). In general, lifestyle intervention is increasingly regarded as an effective strategy for prevention of depression and dementia separately. However, the evidence regarding the association between lifestyle factors and dementia in people with depression is scarce. We add to the evidence that the beneficial effect of healthy lifestyle on dementia was observed in whether general population or people with depression. Of the individual behavioral factors, we only found that physically inactive was significantly associated with higher risk of dementia after the onset of depression, highlighting the critically important role of physical activity as an intervention target for depression and post-depression dementia.

The importance of multimorbidity is increasingly being recognized as its high prevalence at older ages (Barnett et al., 2012). However, a large body of prior studies concentrated on risk factors and prognosis of cardiometabolic multimorbidity (Di Angelantonio et al., 2015; Freisling et al., 2020; Singh-Manoux et al., 2018). The evidence regarding the pattern of neuropsychiatric comorbidity is limited. To the best of our knowledge, our study is the first to examine modifiable lifestyle factors and post-depression dementia. Several overlapping pathophysiological substrates might explain the comorbidity of both syndromes (Linnemann and Lang, 2020). Firstly, a stress syndrome, i.e., elevated cortisol levels, has been observed in up to 70 % of depressed patients and also in Alzheimer's disease pathology (Checkley, 1996). Stress conditions can cause hippocampal neuronal damage as well as cognitive impairment. Secondly, the development of a depression and dementia after the onset of vascular diseases, the profile of cerebrovascular risk factors in both disorders and the impairments depending on the location of cerebrovascular lesions, speak in favor of a vascular hypothesis as a common factor for both disorders (Alexopoulos, 2019). Third, depression seems to accelerate the process of ageing. Studies found that individuals who were or had been depressed had shorter telomere length, indicating their bodies had aged more rapidly, even when all other factors were considered (Verhoeven et al., 2016). In our study, we found that depression and dementia shared common risk factors, such as physical inactive, current smoking and poor diet pattern. In line with our study, separate studies concluded that depression and dementia shared common etiological factors such as inflammation, vascular changes and vascular risk factors (Barnes et al., 2006; Hayley et al., 2021; Kohler et al., 2010).

Our findings need to be considered in light of the study's strengths and limitations. The primary strengths of this study are our analytical strategy that involved 3 transition paths and assessed both etiological and prognostic factors in the same analytical framework, which allowed us to examine the temporal progression from depression to dementia. Another strength of our study is the large sample size and long follow-up, which allowed our study on clinically diagnosed depression and dementia, and the availability of complete data on health outcomes. Despite these strengths, several limitations of the current study need to be considered. First, information on lifestyle factors assessed at baseline was used in this study, while potential changes in lifestyle factors during lifetime, particularly after the onset of depression, could not be accounted for in the investigation. Nevertheless, it has been shown that in the absence of interventions, the vast majority of individuals do not make major lifestyle changes following diagnosis of a serious chronic disease (Newsom et al., 2012). Second, diagnosis of depression and dementia relies on linked electronic health records, which may not capture all participants with clinically significant psychopathology. While the overall accuracy of obtaining dementia diagnoses via registries is good (Wilkinson et al., 2019), misclassification of some study participants remains a possibility. Milder depression or severely depressed people who very hardly go to the hospital unless they are in danger of life may easily be underestimated. Third, although all models were adjusted for known potential biases and participants were followed up for a median of 11.8 years, it is possible that unmeasured confounds and reverse causation remained. Of note, several sensitivity analyses conducted in our study supported the robust of our finding. Finally, given the observational study design, the exact conclusions of causality should be made with caution as residual confounding cannot be ruled out.

In conclusion, both depression and dementia impose a significant burden on public health, more attention should be paid to neuropsychiatric comorbidity. In our study, we found an increased risk of depression and post-depression dementia in people with high-risk lifestyle factors. Our findings further add to the evidence that it is of great significance to integrate comprehensive lifestyle interventions, particularly for regular physical activity, for prevention of both depression and post-depression dementia. Future studies are warranted to clarify the neurobiological mechanisms underlying the links among lifestyle factors and post-depression dementia.

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CRediT authorship contribution statement

Chenjie Xu and Zhi Cao contributed equally to this work.

Chenjie Xu: Data curation, Methodology, Software, Visualization, Writing- Original draft preparation. Zhi Cao: Software, Methodology, Visualization, Writing- Original draft preparation. Xianhong Huang: Reviewing and Editing. Xiaohe Wang: Conceptualization, Investigation, Supervision, Validation, Reviewing and Editing.

Conflict of interest

The authors declare that they have no conflicts of interests.

Data availability

The data that support the findings of this study are available from UK Biobank project site, subject to successful registration and application process. Further details can be found at https://www.ukbiobank.ac.uk/.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2023.01.111.

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