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Research paper

Risk of incident dementia varies with different onset and courses of depression

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ABSTRACT

Background: This study aims to examine if risk of dementia differs between adult- and late-onset depression.
Methods: 16,608 community-living dementia-free older adults were followed for 6 years to the outcome of incident dementia. Depression was diagnosed according to international diagnostic guidelines. Depression in adulthood or late life was categorized using age 65 as cutoff. Hazard ratio for dementia was estimated using Cox regression analysis.
Results: People with depression in adulthood only did not have higher dementia incidence, suggesting those in remission from adult-onset depression are not at greater risk of dementia. Conversely, having depression in both adulthood and late life was associated with higher dementia risk, and improvement in depression in late life was associated with lower risk, suggesting persistent or recurrent lifetime depression is a risk factor for dementia. Those with depression in late life only were not associated with higher dementia risk after controlling for the longitudinal changes in depressive symptoms, consistent with late-onset depression being a prodrome of dementia.
Limitations: Reverse causation is a potential limitation. This was minimized by careful ascertainment of depression and dementia cases, exclusion of individuals with suspected dementia at baseline and those who developed dementia within 3 years after baseline, and controlling for various important confounders.
Conclusions: Risk of incident dementia varies with presence and resolution of depression at different ages. Further studies are needed to test whether treating adult-onset depression may prevent dementia. Older adults with a history of depression present for an extended time should be monitored for cognitive decline.

1. Introduction

Dementia is a major health problem worldwide. Early identification and timely intervention of modifiable risk factors is of great clinical importance in slowing or preventing dementia onset (Livingston et al., 2017). While meta-analyses show that depression is associated with a two-fold increase in risk of dementia (Diniz et al., 2013; Ownby et al., 2006), several key questions remain unanswered. First, depressive symptoms often appear before the clinical manifestation of dementia (Alexopoulos, 2005; Steffens, 2017). Inclusion of these participants would introduce the risk of reverse causation and thus make it difficult to ascertain if depression is a risk factor for or a prodrome of dementia. Second, with depression typically starting in adulthood, the course of illness varies across individuals; and since people with depression tend to have poorer health outcomes and adherence to healthy lifestyle practice, it remains uncertain whether depression in earlier life, chronicity or recurrence of depression in later life, or other health conditions and behaviours contribute most to the observed higher risk of dementia (Almeida et al., 2017; Barnes et al., 2012; Geerlings et al., 2008; Heser et al., 2013; Holmquist et al., 2020; Li et al., 2011; Pálsson et al., 1999).

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Third, prior epidemiological studies often classified depression from self-reported depressive symptoms from depression screening scales (Ezzati et al., 2019; Kaup et al., 2016; Mirza et al., 2016; Norton et al., 2019; Singh-Manoux et al., 2017). Given that there are many conditions with a similar presentation to depression that associate with dementia, misclassifying depression might introduce bias in the observed association. Having a comprehensive clinical assessment to exclude other disorders, with ascertainment of clinical depression based on standardized diagnostic guidelines, might allow us to be more confident about the association.

In this longitudinal observational study, we followed the mood and cognitive status of a large well-characterized cohort of community-living older adults who were free of dementia at baseline. The objective was to examine if the risk of dementia varied with different time of onset and clinical courses of depression, independent of other health-related and lifestyle factors. Our findings might provide additional evidence and new insight to the existing knowledge gap for the nature of association between depression and dementia.

2. Methods

2.1. Study design

This longitudinal observational study was based on individuals attending the Elderly Health Centres (EHCs) of the Department of Health of the Government of Hong Kong. With one centre in each district, the EHCs provide primary care services, including regular physical, mental, and cognitive health assessments, to local older adults in Hong Kong. A total of 18,298 older adults from all 18 EHCs were registered at baseline. Inclusion criteria for this study were age 65 years or older and Chinese ethnicity. Exclusion criteria were having dementia and not completing the assessment of depression at baseline. To minimize potential residual confounding due to suspected dementia, we also excluded participants living in care homes, having history of stroke or Parkinson's disease, or scoring below the education-specific cutoff on the Cantonese version of the Mini-Mental State Examination (C-MMSE) at baseline (Chiu et al., 1998). Participants were followed until the onset of dementia, death, or Year 6, whichever occurred first. Those who missed the follow-up assessments were actively traced and interviewed either at the EHCs, at their homes, or by telephone. The names of those not traceable were verified with the Deaths Registry, with the cause of death, including dementia, identified. Written informed consent was obtained from all participants or from their relatives if they were mentally incapable to give consent before the follow-up assessment was conducted. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Department of Health of the Government of Hong Kong and the Joint Clinical Research Ethics Committee of the Chinese University of Hong Kong and the New Territories East Cluster of the Hospital Authority.

2.2. Assessment of depression

At baseline, all participants were screened for depression. This included review of medical records to identify any history of depression, followed by comprehensive history taking and clinical assessment to ascertain presence of depression at baseline. Depression was defined as clinical diagnosis of depression made by psychiatrists in accordance with the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10). The onset of depression was defined as the time of having clinical diagnosis of depression; onset in adulthood or later life was classified using age 65 as cutoff. Moreover, at baseline and follow-up, all participants completed the Cantonese version of the 15-item Geriatric Depression Scale (GDS), a self-report measure of depression already validated for the Hong Kong Chinese older population (Lee et al., 1993).

2.3. Assessment of dementia

At baseline and follow-up, all participants underwent comprehensive cognitive assessments, including a detailed history and cognitive screening such as the Delayed Recall Test, the Abbreviated Mental Test, and the C-MMSE. Those who missed the follow-up assessments but were traced and interviewed received the C-MMSE, clinical examination, or the Clinical Dementia Rating (CDR), depending on whether the interview was conducted in person or over the phone. Dementia was defined as clinical diagnosis of dementia made by geriatric psychiatrists in accordance with the ICD-10 or a CDR of 1–3. The study outcome was incident dementia over 6 years.

2.4. Assessment of co-variables

Participants' sociodemographics (age, sex, educational level, socioeconomic status), physical comorbidities (hypertension, diabetes, hypercholesterolemia, obesity, heart diseases, visual and hearing impairments, and poor mobility), and lifestyle behaviours (physical, intellectual, and social activities, fruit and vegetable intake, smoking, and alcohol use) were examined during the assessment. Low socioeconomic status was defined as receiving social security from the government. All medical diseases were diagnosed by physicians at the EHCs in accordance with the ICD-10. Hearing impairment was defined as 1- and 2-kHz loss of more than 40 decibels in the better ear during audiometric testing (Audioscope, Welch Allyn). Visual impairment was defined as equal to or greater than 0.48 LogMAR (Lee et al., 2020). Poor mobility was defined as needing an aid to walk or being chairbound. A standardized self-reported questionnaire based on locally validated leisure activity classification was used to assess lifestyle behaviours in the prior month, with regular participation in physical, intellectual, and social activities, adequate daily consumption of fruits and vegetables, current smoking, and alcohol use defined as previously reported (Lee et al., 2018).

2.5. Sample size estimation

Sample size estimation was performed using the Power and Precision software, version 3.0 (Biostat). Sample size was calculated based on depression increasing the risk of dementia by two-fold and estimates of incidence rate of dementia from previous local data (6% in 6 years). With alpha set at 0.05, a baseline sample of 10,000 participants would yield at least 80% power for detection of dementia at follow-up.

2.6. Statistical analysis

Statistical analysis was performed using the IBM SPSS Statistics, Version 24.0 (IBM Corp). The number of participants with follow-up during the 6-year study period was expressed as person-years, which was calculated by summing each participant's contribution of follow-up time. Based on presence of depression at different life stages, we categorized depression into 4 groups: (i) no depression in adulthood or in late life (i.e., free of clinical depression in their lifetime); (ii) depression in adulthood, but not in late life (in remission from adult-onset depression); (iii) depression in both adulthood and late life (persistent depression); and (iv) no depression in adulthood, but depression in late life (late-onset depression). Dementia incidence and differences in baseline variables between participants with and without incident dementia in each group of depression were analyzed, with the latter by the independent *t*-test or the χ^2 test, as appropriate. The level of statistical significance was set at $p < 0.05$ (2-tailed).

To minimize the possibility of reverse causality, we repeated the analyses by selecting participants who were still free of dementia at Year 3 (i.e., excluding those who developed dementia within 3 years after baseline and those who could not be confirmed to be still free of dementia by Year 3 owing to missing the interim follow-up assessment).

We chose 3 years because older adults often develop dementia within 3 years after depression (Alexopoulos, 2019), and the risk of dementia reduces significantly beyond this timeframe (Steffens et al., 1997).

To identify the risk of incident dementia in each group of depression, Cox proportional hazards regression analyses were conducted to estimate the unadjusted Hazard Ratio (HR) for incident dementia for each group, with the first group (the group who never had depression) serving as control. To ascertain that any observed association with higher dementia risk was explained by depression at a particular life stage rather than worsening of depressive symptoms prior to dementia onset, the trajectories of GDS score from baseline to Year 3 were compared within and between those with and without incident dementia at Years 4 to 6, using paired *t*-test and General Linear Model repeated measures, respectively, and the baseline GDS score and the longitudinal changes of GDS score over the first 3 years were controlled for in the regression analyses. Also, to ascertain that the observed association was independent of the confounding effect, age, sex, educational level, socioeconomic status, hypertension, diabetes, hypercholesterolemia, obesity, heart diseases, visual impairment, hearing impairment, poor mobility, physical exercise, intellectual activities, social activities, fruit and vegetable consumption, smoking, and drinking were additionally adjusted for in the regression analyses.

Moreover, to test if improvement of depressive symptoms in late life was associated with lower dementia risk, sensitivity analysis was performed to estimate the HRs for incident dementia at Years 4 to 6 in participants whose GDS score decreased from ≥8 at baseline to <8 by Year 3.

3. Results

A total of 16,608 older adults (90.8%) constituted the present study sample (see Supplementary Figure 1 for the flowchart of this study). They had a median follow-up period of 5.0 years (interquartile range, 3.0–6.0 years), contributing 73,120 person-years of follow-up over the 6-year study period. Of these, 1,432 (8.6%) developed incident dementia in 6 years. Dementia incidence and differences in baseline characteristics between those with and without incident dementia in 6 years for different groups of depression were shown in Table 1.

3.1. Risk of dementia in older adults with past history of depression in adulthood

The proportion of participants with adulthood-only depression was not significantly higher in those with incident dementia at Years 4 to 6 than in those without (17 of 746 [2.3%] vs 204 of 10,972 [1.9%]; $p = 0.42$). Their baseline GDS score was not higher in the incident dementia group than in the cognitively stable group ($p = 0.61$), and the longitudinal changes of GDS score over the first 3 years did not differ between the two groups (incident dementia group: 2.8 [SD = 2.1] at baseline vs 2.9 [3.2] at Year 3, $p = 0.80$; cognitively stable group: 3.1 [2.4] at baseline vs 3.4 [3.1] at Year 3, $p = 0.22$; between group differences over time, $p = 0.22$; Supplementary Figure 2). Adulthood-only depression had an unadjusted HR of 1.23 (95% CI = 0.75–2.03, $p = 0.42$; Model 1 in Table 2) and an adjusted HR of 0.96 (95% CI = 0.55–1.69, $p = 0.89$; Model 2 in Table 2) for incident dementia at Years 4 to 6.

Table 1
Differences in baseline characteristics between participants with and without incident dementia in 6 years.

Baseline characteristics	No depression			Adulthood-only depression			Persistent depression			Late-onset depression		
	Incident dementia		*p*-value	Incident dementia		*p*-value	Incident dementia		*p*-value	Incident dementia		*p*-value
	No (n = 14171)	Yes (n = 1284)		No (n = 293)	Yes (n = 38)		No (n = 288)	Yes (n = 47)		No (n = 424)	Yes (n = 63)	
Age, mean (SD)	74.2(4.7)	76.5 (5.2)	<0.001	73.9 (4.5)	74.8 (5.5)	0.27	75.1 (5.0)	76.0 (4.5)	0.24	75.7 (5.8)	75.1 (4.9)	0.51
Female, n (%)	8772 (61.9)	921 (71.7)	<0.001	225 (76.8)	27 (71.1)	0.44	222 (77.1)	41 (87.2)	0.12	312 (73.6)	52 (82.5)	0.13
No schooling received, n (%)	3539 (25.0)	473 (36.8)	<0.001	85 (29.0)	11 (28.9)	0.99	110 (38.3)	23 (48.9)	0.17	140 (33.0)	28 (44.4)	0.08
On social welfare, n (%)	1658 (11.7)	168 (13.1)	0.14	236 (80.5)	31 (81.6)	0.88	93 (32.3)	18 (38.3)	0.42	315 (74.3)	49 (77.8)	0.55
Hypertension, n (%)	9079 (64.1)	909 (70.8)	<0.001	190 (64.8)	18 (47.4)	0.04	177 (61.5)	27 (57.4)	0.60	252 (59.4)	39 (61.9)	0.71
Diabetes mellitus, n (%)	2087 (14.7)	232 (18.1)	0.001	51 (17.4)	5 (13.2)	0.51	49 (17.0)	10 (21.3)	0.48	66 (15.6)	14 (22.2)	0.18
Hypercholesterolemia, n (%)	5943 (41.9)	555 (43.2)	0.37	151 (51.5)	18 (47.4)	0.63	111 (38.5)	16 (34.0)	0.56	158 (37.3)	28 (44.4)	0.27
Obesity, n (%)	5388 (38.0)	503 (39.2)	0.42	113 (38.6)	13 (34.2)	0.60	89 (31.0)	19 (40.4)	0.20	156 (37.0)	26 (41.3)	0.51
Heart disease, n (%)	1540 (10.9)	182 (14.2)	<0.001	46 (15.7)	5 (13.2)	0.68	44 (15.3)	3 (6.4)	0.10	64 (15.1)	12 (19.0)	0.42
Visual impairment, n (%)	4470 (31.5)	552 (43.0)	<0.001	102 (34.8)	13 (34.2)	0.94	118 (41.0)	31 (66.0)	0.001	212 (50.0)	37 (58.7)	0.20
Hearing impairment, n (%)	3164 (22.3)	324 (25.2)	0.02	74 (25.3)	5 (13.2)	0.10	81 (28.1)	16 (34.0)	0.41	103 (24.3)	19 (30.2)	0.32
Poor mobility, n (%)	931 (6.6)	153 (11.9)	<0.001	31 (10.6)	7 (18.4)	0.15	49 (17.0)	10 (21.3)	0.48	95 (22.4)	16 (25.4)	0.60
Physical exercises, n (%)	6843 (51.3)	507 (41.7)	<0.001	128 (47.1)	13 (39.4)	0.40	91 (37.1)	13 (32.5)	0.57	145 (39.1)	16 (28.1)	0.11
Intellectual activities, n (%)	9676 (68.3)	673 (52.4)	<0.001	178 (60.8)	16 (42.1)	0.03	118 (41.0)	12 (25.5)	0.04	184 (43.4)	23 (36.5)	0.30
Social activities, n (%)	10881 (76.8)	990 (77.1)	0.80	231 (78.8)	35 (92.1)	0.05	207 (71.9)	39 (73.0)	0.11	290 (68.4)	50 (79.4)	0.08
Adequate intake of fruits and vegetables, n (%)	7067 (49.9)	591 (46.0)	0.008	129 (44.0)	16 (42.1)	0.82	80 (27.9)	16 (34.0)	0.39	134 (31.6)	19 (30.2)	0.82
Smoking, n (%)	724 (5.1)	62 (4.8)	0.66	14 (4.8)	0 (0)	0.17	29 (10.1)	4 (8.5)	0.74	24 (5.7)	1 (1.6)	0.17
Drinking, n (%)	596 (4.2)	46 (3.6)	0.28	8 (2.7)	1 (2.6)	0.97	10 (3.5)	1 (2.1)	0.63	15 (3.5)	1 (1.6)	0.42
GDS, mean (SD)	1.3 (1.7)	1.6 (1.8)	<0.001	3.3 (2.5)	3.3 (2.5)	0.96	10.4 (1.9)	10.1 (1.7)	0.25	9.7 (1.7)	10.0 (1.8)	0.24

Table 2
Estimated hazard ratios (HRs) and 95% confidence intervals (95% CI) for incident dementia at Years 4 to 6.

	Model 1 HR (95% CI)	*p*-value	Model 2 HR (95% CI)	*p*-value
No depression	Reference		Reference	
Adulthood-only depression	1.23 (0.75–2.03)	0.42	0.96 (0.55–1.69)	0.89
Persistent depression	1.15 (1.11–1.19)	<0.001	1.13 (1.05–1.21)	0.001
Late-onset depression	1.97 (1.36–2.85)	<0.001	0.91 (0.56–1.47)	0.69

Model 1: Unadjusted.
Model 2: Adjusted for baseline GDS score, longitudinal GDS changes over the first 3 years, and other potential confounding factors including age, sex, educational level, socioeconomic status, hypertension, diabetes, hypercholesterolemia, obesity, heart diseases, visual impairment, hearing impairment, poor mobility, physical exercise, intellectual activities, social activities, fruit and vegetable consumption, smoking, and drinking.

3.2. Risk of dementia in older adults with persistent depression

The proportion of participants with persistent depression was higher in the incident dementia group at Years 4 to 6 than in the cognitively stable group (28 of 757 [3.7%] vs 172 of 10,940 [1.6%], $p < 0.001$). Their baseline GDS score was not significantly different between those with and without incident dementia at Years 4 to 6 ($p = 0.75$), and both showed a decline in GDS score over the first 3 years (incident dementia group: 10.3 [SD = 1.7] at baseline vs 8.6 [3.5] at Year 3, $p = 0.01$; cognitively stable group: 10.2 [1.9] at baseline vs 7.0 [4.3] at Year 3, $p < 0.001$; between group differences over time, $p = 0.03$; Supplementary Figure 3). Persistent depression had an unadjusted HR of 1.15 (95% CI = 1.11–1.19, $p < 0.001$; Model 1 in Table 2) for incident dementia at Years 4 to 6. The association remained significant after adjusting for baseline GDS score, longitudinal GDS changes over the first 3 years, and all the potential confounding factors (adjusted HR = 1.13, 95% CI = 1.05–1.21, $p = 0.001$; Model 2 in Table 2).

Compared to participants whose GDS score maintained ≥8 by Year 3, those with GDS < 8 by Year 3 had lower risk of dementia at Years 4 to 6 (unadjusted HR = 0.39, 95% CI = 0.17–0.89, $p = 0.03$; adjusted HR = 0.35, 95% CI = 0.14–0.91, $p = 0.03$).

3.3. Risk of dementia in older adults with late-onset depression

The proportion of participants with late-onset depression at baseline was higher in the incident dementia group at Years 4 to 6 than in the cognitively stable group (33 of 762 [4.3%] vs 248 of 11,016 [2.3%]; $p < 0.001$). Their baseline GDS score was not significantly different between those with and without incident dementia at Years 4 to 6 ($p = 0.33$), whereas the longitudinal changes of GDS score over the first 3 years were (incident dementia group: 10.0 [1.9] at baseline vs 6.9 [3.5] at Year 3, $p < 0.001$; cognitively stable group: 9.7 [1.7] at baseline vs 5.4 [3.5] at Year 3, $p < 0.001$; between group differences over time, $p = 0.04$; Supplementary Figure 4). Late-onset depression had an unadjusted HR of 1.97 (95% CI = 1.36–2.85, $p < 0.001$; Model 1 in Table 2) for incident dementia at Years 4 to 6, but the association was no longer significant after adjusting for baseline GDS score, longitudinal GDS changes over the first 3 years, and the same potential confounding factors (adjusted HR = 0.91; 95% CI = 0.56–1.47, $p = 0.69$; Model 2 in Table 2). Conversely, the association between the longitudinal GDS changes and higher dementia risk remained significant even when controlled for baseline GDS score, late-onset depression, and the same confounders (adjusted HR = 1.10; 95% CI = 1.05–1.15; $p < 0.001$).

Compared to participants whose GDS score maintained ≥8 by Year 3, those with GDS < 8 by Year 3 did not show lower risk of incident dementia at Years 4 to 6 (unadjusted HR = 0.58, 95% CI = 0.29–1.15, $p = 0.18$; adjusted HR = 0.53, 95% CI = 0.24–1.19, $p = 0.12$).

3.4. Risk of dementia in older adults who never had depression

In participants without depression in their lifetime ($n = 11,497$), the baseline GDS score was higher in the incident dementia group than in the cognitively stable group ($p < 0.001$). However, a longitudinal increase in GDS score was observed in both groups (incident dementia group: 1.6 [1.8] at baseline vs 1.9 [2.1] at Year 3, $p < 0.001$; cognitively stable group: 1.3 [1.6] at baseline vs 1.4 [1.9] at Year 3, $p < 0.001$), with the rate of increase being higher in the incident dementia group than in the cognitively stable group ($p < 0.001$; Supplementary Figure 5). Baseline GDS score was not associated with higher risk of incident dementia at Years 4 to 6 after controlling for the longitudinal GDS changes over the first 3 years and the same potential confounding factors (adjusted HR = 0.97, 95% CI = 0.91–1.05, $p = 0.46$), whereas the longitudinal GDS changes were (adjusted HR = 1.11, 95% CI = 1.03–1.19; $p = 0.007$).

4. Discussion

In this study, we found that people who only had depression in adulthood did not have higher dementia incidence, suggesting that those in remission from adult-onset depression are not at greater risk of dementia. Conversely, having depression in both adulthood and late life was associated with higher dementia incidence, and improvement in depression in late life was associated with lower incidence; these suggest that persistent or recurrent lifetime depression is a risk factor for dementia. Additionally, having depression only in late life was not associated with higher dementia risk after controlling for the longitudinal changes in depressive symptoms, consistent with late-onset depression being a prodrome of dementia. Our study shows that the risk of incident dementia varies with presence and resolution of depression at different ages. From a clinical perspective, our findings highlight the need to closely monitor cognitive decline in older adults with a history of depression present for an extended period of time and to test whether treating adult-onset depression may prevent dementia.

4.1. Comparison with previous studies

The present findings are consistent with the past epidemiologic observation that depression is associated with higher dementia incidence. However, to our knowledge, previous studies did not adequately examine the nature of the observed association. Nor did they address the possibility of reverse causality, confounding effect, and misclassification error. Based on the past findings, it was therefore uncertain whether depression is a risk factor for or an early sign of dementia. The present study is better controlled than previous studies, with consideration of the important confounders and limitations in the study design and analysis. Our findings highlight not only a difference in the risk of dementia across depression of different onset and courses, but also, from a public health perspective, the need to promote inclusion of depression assessment into dementia screening.

We observed a small but significant increase in depressive symptoms with time in older adults without clinical depression in their lifetime, with the rate of increase being higher in the incident dementia group. These were not fully explained by baseline GDS score and confounding factors. Our findings suggest that late-life mood changes may be a prodrome of dementia, and healthcare professionals need to be mindful of the possibility of neurodegeneration developing in older adults who are increasingly depressed, even when the mood symptoms are only subclinical.

While late-onset depression was more prevalent in the incident dementia group, its association with higher dementia incidence appears to be explained by the longitudinal changes in depressive symptoms prior to dementia onset rather than depression at baseline. More importantly,

in those with late-onset depression, improvement of depressive symptoms was not associated with lower risk of dementia. These findings suggest that similar to subclinical depressive symptoms, late-onset depression may be a marker of incipient dementia rather than a risk factor.

Interestingly, adulthood-only depression was not associated with higher dementia incidence. The mean GDS score of older adults who were no longer depressed was not higher in the incident dementia group, and the longitudinal changes of the GDS score in late life were not different between those with and without incident dementia. These findings suggest that people in remission from adult-onset depression might not be at greater risk of dementia in their later life. It would be of great clinical importance to conduct further studies to test whether treating adult-onset depression prevents dementia in late life.

In contrast, older adults with depression in both adulthood and late life were associated with higher dementia incidence. However, compared to those with late-onset depression, this association was not explained by the longitudinal changes of the GDS score in late life. More importantly, and consistent with the findings for adulthood-only depression, we found that improvement of depressive symptoms in late life was associated with lower risk of dementia. Our findings suggest that persistent or recurrent lifetime depression might be a risk factor rather than a prodromal sign of dementia. Although this study did not investigate underlying mechanisms, we speculate that long chronicity and frequent relapse of depression may impair cognitive function as a result of long-standing and repeated insults to the brain mediated by dysregulation of stress hormones in the hypothalamic-pituitary-adrenal (HPA) axis, neuronal growth factors such as brain-derived neurotrophic factor (BDNF), inflammatory and immune responses, and impaired cerebral blood flow (Alexopoulos, 2019). These are associated with neurodegenerative pathologies, including hippocampal atrophy, amyloid deposition, cerebrovascular lesions, and altered structural and functional connectivities (Agudelo et al., 2015; Dafsari and Jessen, 2020). With antidepressants having the potential to reduce amyloid load (Sheline et al., 2014), promote neurogenesis (Planchez et al., 2020), and moderate inflammation (Walker, 2013), early identification and treatment of depression might serve as a useful risk reduction strategy.

4.2. Strengths and limitations

This study had several strengths. We followed this large territory-wide community cohort for a long time, with a low attrition rate. We used comprehensive and in-depth clinical interviewing to ascertain depression and dementia cases, examined the history and longitudinal course of depression, and addressed the possibility of reverse causality. Also, a wide range of health problems and behaviours were included.

Nevertheless, this study had some limitations. First, the possibility of reverse causation, though minimized, could not be completely excluded because of the observational nature of the study and the lack of information on baseline cognitive capacities, details of adulthood depression (exact age of onset, severity, and number of episodes), and treatment of depression (type, duration, and compliance). While the observed association remained significant after excluding participants who developed dementia within 3 years after baseline, and the longitudinal mood changes were different across groups, the potential confounding problem of depression being an early manifestation of preclinical dementia might still be present. Hence, care needs to be taken when making an inference about a causal association between depression and dementia. Second, the clinical diagnosis of depression in adulthood was based on retrospective review of medical records, and stratification of depression into different subgroups might introduce the problems of multiple comparisons and loss of power, in particular when examining the risk of dementia in those with both earlier- and late-life depression. Nevertheless, type I error is unlikely, as the associations remained robust after controlling for the longitudinal GDS changes and various confounders, and previous epidemiological studies also reported recurrent depression associating with higher dementia incidence (Dotson et al., 2010; James et al., 2018). Third, genotyping and neuroimaging were not performed in this study, thus limiting us from examining if depression is associated with a particular subtype of dementia. Last, caution should be exercised when generalizing our findings to older populations of other ethnicities or with more comorbidities, because our participants were ethnic Chinese, had a relatively lower educational level, and were relatively healthy.

5. Conclusion

Depending on the time of onset and course of depression, its association with risk of dementia differs. Our findings suggest that those with depression in late life might warrant further dementia risk assessment and management. Future trials to test whether treatment of depression in earlier life reduces subsequent risk of dementia will provide additional insight to the causality between the two and highlight its clinical significance in dementia prevention.

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Author contributions

All authors meet ICMJE criteria for authorship. ATCL, MR, WCC, HFKC, RSYL, and LCWL conceived of and designed the study. ATCL and AWTF searched the literature and collected and analyzed the data. ATCL interpreted the data, wrote the paper, and prepared the figures. AWFT, MR, WCC, HFKC, RSYL, and LCWL critically edited and revised the work, interpreted the data, and approved the final version to be submitted for publication. LCWL obtained the funding and supervised the study.

The corresponding author (LCWL) has full access to all the data in the study and has the final responsibility for the decision to submit for publication.

Data availability

The data that support the findings of this study are available from the corresponding author, LCWL, upon reasonable request. The data are not publicly available due to concern of comprising the privacy of participants.

Declaration of Competing Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2020.12.195.

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