Depression duration and risk of incident cardiovascular disease: a population-based six-year cohort study

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ABSTRACT

*Background***:** Depression symptoms are significantly associated with an increased risk of cardiovascular disease (CVD). However, understanding of the magnitude of the association between depression duration and risk of CVD is limited. Therefore, we aimed to assess whether a longer duration of exposure to depression is associated with a higher risk of new-onset CVD.

*Methods***:** A territory-wide population-based longitudinal cohort study of patients with depression diagnosis aged 10 years and above in a public healthcare system in Hong Kong. The study period spanned January 1, 2014, to December 31, 2019, and all participants had no CVD at baseline. Incidence of CVD was calculated. We used Cox proportional hazard regression to adjust confounders and estimate hazard ratios of CVD risk.

*Results***:** Among the patients with depression, 1,306 individuals developed CVD. Multi-adjusted models showed individuals with depression duration of 2–5 years (Hazard ratios [HRs]: 1.38 [95% confidence interval (CI): 1.19–1.60]) and ≥6 years (1.45 [1.25–1.68]) had a significantly escalated risk of developing CVD, compared with those with depression duration of 0–1 year. Stratified analyses indicated that the association was significant in women and those under 65 years old.

Limitations: Electronic medical records based retrospective study without depression severity measurement, limited sample size for some subgroup analyses.

*Conclusions***:** Longer exposure to depression is associated with significant increased risk of CVD. The interplay between mental and vascular health emphasizes the need for CVD prevention in patients with long-term depression.

Keywords: Depression duration, cardiovascular disease, electronic health records

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1. Introduction

As a leading cause of health loss, depression is associated with various medical disorders and a considerable burden on the healthcare system (Nemeroff, 2012; GBD 2017 Disease and Injury Incidence and Prevalence Collaborator, 2018). A multitude of research has shown that depression adversely affects the cardiovascular system and is related to the occurrence of cardiovascular diseases (CVD) and the consequent mortality (Baune et al., 2012; Harshfield et al., 2020; Meng et al., 2020). Important biological factors contributing to the development of CVD in depressive patients include increased inflammation and endocrine disturbances (Nemeroff, 2012; Baune et al., 2012). Duration of depression, as a marker of exposure to these biological risk factors, may play an important role in the development of CVD following depression (Baune et al., 2012).

Research on the association between depression duration and risk of CVD is limited to specific age or sex groups with inconsistent findings. A Swedish twin study showed that the risk of coronary artery disease in middle-aged and older adults increased 2.5-fold at the same year of major depression onset and 1.2-fold in subsequent years, after adjusting for genetic factors of the two diseases (Kendler et al., 2009). A prospective cohort study from the U.S. showed that, compared with men aged 70 and above without depression, those with depression diagnosed within three years had a higher risk of developing congestive heart failure, stroke, and coronary heart disease (Penninx et al., 1998). However, another longitudinal Swedish male cohort study showed that depression onset before 21 years old did not predict the risk of subsequent coronary heart disease and acute myocardial infarction in middle age

(Janszky et al., 2010). Also, a cross-sectional study from the Netherlands showed that the duration of depressive or anxious symptoms was not related to the risk of coronary heart disease (Vogelzangs et al., 2010). Evidence about sex and age differences in association with depression duration and CVD risk is lacking. Investigating these differences will be beneficial in clinical practice for CVD prevention in people living with depression.

To our best knowledge, few studies have investigated how depression duration would impact the risk of subsequent CVD in Asian societies which have the high prevalence of depression and cardiovascular disease (WHO, 2008; Ohira et al., 2013). To bridge these gaps, we aimed to investigate the association between duration of depression and subsequent CVD using a territory-wide population-based longitudinal depression cohort in Hong Kong.

2. Methods

2.1 Data source and target population

Data were collected from the Clinical Data Analysis and Reporting System (CDARS), a territory-wide electronic health record database in Hong Kong. This database is managed by the Hospital Authority of Hong Kong, the statutory body that manages all public hospitals and primary care clinics. Public hospitals in Hong Kong provide approximately 80% of inpatient department visit services and almost all Accident and Emergency department visit services (Food and Health Bureau of Hong Kong Special Administrative Region Government, 2017). The Hospital Authority is also a cardinal provider of mental health medical services, including inpatient, outpatient, psychiatric, and community services (Food and Health Bureau of Hong Kong Special Administrative Region Government, 2017). A detailed description of the data source

and epidemiological studies have been published elsewhere (Chai et al., 2020; Man et al., 2017). This study has received ethics approval from the Institutional Review Board of The University of Hong Kong/Hospital Authority Hong Kong Western Cluster (UW 20-218). Personal information is de-identified in the CDARS database for privacy protection.

Patient data were retrieved from CDARS if they were diagnosed with depression in inpatient, accident and emergency, and outpatient settings (the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes of depression include 296.2, 296.3, 300.4, and 311) from January to December 2014. The date of the first depression diagnosis in 2014 was set as the index date. Patients were excluded if they: (1) had a history of CVD diagnosis before or on the index date; (2) were aged younger than 10 years; (3) had missing information on the date of birth; (4) had incorrectly entered follow-up time (date of death was earlier than the date of index date due to database error); and (5) died on the index date (Figure 1).

2.2 Study design

In this study, we followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement (von Elm et al., 2007). Patients were followed up from the index date in 2014 until the onset of CVD, death (all-cause), or end of study follow-up (December 31, 2019), whichever came first. Details of this retrospective cohort study is shown in electronic supplementary material: Figure 1.

2.3 Measures

Outcome measure. The outcome was incident CVD, the initial presentation of any CVDs diagnosed in outpatient, Accident and Emergency, inpatient setting, or at death. This consisted of ischemic heart disease, cerebrovascular disease, emboli and thrombosis, heart failure, arrhythmia/conduction disorder, and other subtypes

(McCarron et al., 2000; Song et al., 2019). The detailed ICD-9 codes for CVD are reported in electronic supplementary material: Table 1.

Duration of depression. Duration of depression was the interval between the date of the first record of depression diagnosis since 1 January 2004 and the index date in 2014, classified in three groups: 0–1 year, 2–5 years, and 6 and above years.

Covariates. Potential confounders of the association between depression duration and CVD included sex, age, history of hypertension, diabetes (Damen et al., 2016), cancer (Koene et al., 2016), psychiatric comorbidities (a combination of eight mental disorders, including anxiety disorder, suicidal ideation or intention, psychosis, personality disorder, epilepsy, schizophrenia, attention deficit hyperactivity disorder, and autism). Psychiatric comorbidity was added as a covariate as it may be closely associated with the cardiovascular outcomes (Riba et al., 2012). Detailed ICD-9 codes for the covariates are also reported in electronic supplementary material: Table 1.

2.4 Statistical analysis

Main analysis. Comparisons of demographics and clinical characteristics between depression patients with and without CVD were conducted using $\chi 2$ (categorical variables), t test (continuous variables), and Fisher's exact test (variables with small frequencies, e.g., autism, attention deficit hyperactivity disorder). Incidence of CVD per 1000 person years during follow-up using Poisson distribution with 95% confidence interval was calculated. Cox proportional hazard regression was fitted to calculate hazard ratios (HRs) and 95% confidence intervals for the risk of CVD. We tested the proportional-hazards assumption using Schoenfeld residuals. The interaction terms of depression duration with sex and age were respectively added to the Cox model to test the effects of sex and age on the risk of CVD within each group of depression duration.

Subgroup and sensitivity analysis. We conducted subgroup analysis to examine the risk of CVD in subgroups stratified by sex and age (<65 versus ≥65 years). In sensitivity analyses, we investigated the risk of subsequent CVD by treating depression duration as a continuous variable. Also, given the long asymptomatic characteristic of CVD between illness onset and symptomatic manifestation (Ziegelstein, 2017), participants who developed CVD within one year after the index date were excluded. It was an effort to reduce the possibility that CVD diagnosed within one year during follow-up had developed but was not recorded before the index date due to its asymptomatic characteristic. Additionally, to account for the competing risk from death, we used the Fine and Gray hazard models to assess the subdistribution hazard ratio of CVD. Finally, using E-value methodology (VanderWeele & Ding, 2017), we assessed the robustness of this association to the unmeasured confounders. $P<.05$ was defined as statistical significance (two-tailed). All analyses were cross-checked by two researchers independently and carried out using R Version 4.0.5 (R Core Team, 2021).

3. Results

A total of 11,651 individuals with depression met inclusion criteria for the analysis. Among them, 1,306 (11.2%) developed CVD and 831 (7.1%) died during a median follow-up of 5.5 years (61,475 person-years) (Figure 1). Table 1 shows the characteristics of the study cohort and the comparisons between depression patients with and without CVD. In the current cohort (mean age: 48.0 years and 74.4% women), around 75.8% had a duration of depression of 0–1 year. The prevalence of hypertension, diabetes, and cancer at baseline were 8.9%, 5.3%, and 8.6%, respectively. Approximately 20.8% of patients had at least one psychiatric

comorbidity. The most common psychiatric comorbidity was suicidal ideation or intention (9.5%), followed by anxiety disorder (8.2%), and psychosis (3.8%). As shown in Table 1, individuals who developed CVD were more likely to be older, with longer depression duration (19.1% with depression duration ⩾ 6 years), and have traditional cardiovascular risk factors, including hypertension (25.0%), diabetes (14.3%), and cancer (13.0%), than those who remained CVD-free.

The overall incidence of CVD in patients with depression was 22.39 (21.19–23.64) per 1000 person-years (Table 2). Individuals with longer depression duration were more likely to develop incident CVD over time (Figure 2). Besides, the CVD incidence showed dose-response with the depression duration. The incidence of CVD was also found to be greater in men and those aged 65 and above (Table 2).

In the main analysis, the risk of subsequent CVD was significantly higher among patients with a duration of depression of 2–5 years (adjusted HR: 1.38 [1.19–1.60]) and 6 and above years (adjusted HR: 1.45 [1.25–1.68]) compared with those with the duration of 0–1 year, after controlling for covariates (Figure 3). Age but not sex showed significant interaction with depression duration (see electronic supplementary material: Table 2).

In the subgroup analyses, the significant association between duration of depression and risk of new-onset CVD was observed in women (2–5 years vs. 0–1 year: HR 1.40 [1.16–1.68]; 6 and above years vs. 0–1 year: HR 1.53 [1.29–1.82]), and a significant association in men only appeared in the depression duration of 0–1 year (HR 1.34 [1.03–1.76]) (Figure 4). In addition, the association was significant in those younger than 65 (2–5 years vs. within 1 year: HR 1.66 [1.35–2.03]; 6 and above years vs. within 1 year: HR 1.77 [1.44–2.18]), but not in those aged 65 and above (Figure 5). The same patterns of the association between duration of depression and CVD were

found in a series of sensitivity analyses using continuous measure of depression duration (see electronic supplementary material: Table 3), using the Fine and Gray model to adjust for competing risk (see electronic supplementary material: Table 4), or excluding those diagnosed with CVD within one year during follow-up (see electronic supplementary material: Table 5). The E-values (hazard ratio) for the point estimate and lower confidence interval bound of depression duration of 2-5 and 6+ for incident CVD were 2.10 and 1.67, 2.26 and 1.81, respectively.

4. Discussion

Using territory-wide longitudinal medical records, we found that depression duration was significantly associated with increased risk of CVD after controlling for well-established vascular risk factors. The incidence of CVD in patients with depression reported in this study was similar to that in a diabetes cohort in Hong Kong (23.4 per 1000 person-years) (Wan et al., 2020), an indication that the prevention of CVD in patients with mental disorders should be given as much consideration as those with somatic conditions.

It is well known that inflammation is closely associated with the pathogenesis and prediction of CVD events (Ridker et al., 2000; Libby and Theroux, 2005). Compared with those without depression, individuals with depression had higher inflammation levels across different sex and age (Danner et al., 2003; Penninx et al., 2003; Empana et al., 2005; Vaccarino et al., 2007). The sustained and increased inflammatory reaction in patients with depression might explain the elevated risk of cardiovascular outcome among participants with a longer exposure to depression.

Additionally, our results showed that duration of depression was significantly associated with the risk of CVD in women but not in men after considering the

competing risk and asymptomatic characteristic of CVD. Depression and its comorbidity with CVD are particularly common among women (Möller-Leimkühler, 2010; Malhi and Mann, 2018). Compared with men, traditional cardiac risk factors may be more likely to contribute to CVD in women (Möller-Leimkühler, 2007). Women also have higher susceptibility to inflammation and have higher levels of inflammation (Derry et al., 2015). Combined, a longer duration of depression might contribute to a higher level of cumulative inflammation in women, which might adversely impact their vascular health.

Some scholars hypothesize that depression in older adults may be associated with an elevated risk to the cardiovascular system due to pronounced behavioral changes (e.g., lack of medication compliance and unfavorable lifestyles) related to depressive disorder (Baune et al., 2012). However, age-stratified analysis in this study indicated that depression duration only had a positive association with CVD in those aged 65 or below. A possible explanation might be the difference in inflammation levels between early-onset (having the first clinical presentation of depression before 60) and late-onset depression (having the first clinical presentation of depression at age 60 or older) (Diniz et al., 2010). In the current study, around 95% patients ≥65 years at cohort entry had their first depression diagnosis at 60 years or older, which indicates that almost all had the likelihood of late-onset depression. In contrast, almost 93% of patients under 65 at cohort entry had their first depression diagnosis before 60 years, indicating that most might have had early-onset depression (see electronic supplementary material: Table 6). A previous clinical epidemiological study suggested that patients with early onset depression had higher interleukin 1β serum levels, one of the most predominant inflammatory biomarkers, compared with those with late-onset depression (Diniz et al., 2010). It is speculated that given the same

exposure time to depression, the adverse contribution of inflammation to the cardiovascular system is greater in patients with early-onset depression than late-onset; hence further explaining the different age-effects of depression duration on the risk of CVD in our study.

Clinical practice guidelines suggest that people living with mental health problems should be defined as a disadvantaged group with high CVD risk (National Institute for Health and Care Excellence, 2008), requiring special attention when identifying and assessing CVD risk (National Institute for Health and Care Excellence, 2014). During the consultation and clinical assessment of patients with depression, healthcare professionals should consider how long patients have lived with depression and the subsequent cardiovascular risk. This is particularly important for women and patients with early-onset depression. Preventive management should be initiated to control cardiac risk factors. Policymakers should provide cost-effective, targeted prevention measures to reduce the risk of CVD in people with long exposure to depression.

Study limitations. First, although, we controlled for well-established cardiovascular risk factors, several clinical characteristics (including biomarkers of inflammation, severity of depression, and pharmacotherapy of depression), lifestyle, and socioeconomic status of patients with depression, were unavailable. These factors have been shown to have a close relationship with future risk of CVD (Vaccarino et al., 2007; Nemeroff, 2012; Baune et al., 2012). However, results from E-values showed that it may be implausible to find such unmeasured covariates with the large associations with both depression duration and risk of incident CVD, because they are larger than those of well-known risk factors, such as hypertension and diabetes (Figure 3). Second, we used approximately a decade of diagnosis records to calculate depression duration, which limited the variation range of the “true” length of

depression exposure. Third, the mechanisms underlying the association between depression duration and incident CVD are mainly from limited biological evidence. Clinical and epidemiology research on the association between depression duration and CVD risk and the differences in sex and age is needed.

In conclusion, there is a positive association between depression duration and incident CVD, particularly in women and individuals younger than 65 years. This emphasizes the importance of prevention of CVD in patients with long exposure to depression.

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Table 1.
The characteristics at cohort entry and the comparisons between patients with and without CVD.

Characteristics	Total cohort N = 11651 *N* (%)/mean (SD)	With CVD a N = 1306 *N* (%)/mean (SD)	Without CVD a N = 10345 *N* (%)/mean (SD)	*p* value
Sex				
Men	2986 (25.63)	420 (32.16)	2566 (24.80)	<0.001
Women	8665 (74.37)	886 (67.84)	7779 (75.20)	
Age, y	48.04 (17.21)	62.40 (16.71)	46.23 (16.40)	<0.001
Age distribution, y				
Younger than 65	9702 (83.27)	712 (54.52)	8990 (86.90)	<0.001
65 and older	1949 (16.73)	594 (45.48)	1355 (13.10)	
Duration of depression				
0-1 year	8828 (75.77)	835 (63.94)	7993 (77.26)	<0.001
2-5 years	1435 (12.32)	221 (16.92)	1214 (11.74)	
6 and above years	1388 (11.91)	250 (19.14)	1138 (11.00)	
Hypertension	1041 (8.93)	326 (24.96)	715 (6.91)	<0.001
Diabetes	619 (5.31)	187 (14.32)	432 (4.18)	<0.001
Cancer	1006 (8.63)	170 (13.02)	836 (8.08)	<0.001
Psychiatric comorbidity	2427 (20.83)	282 (21.59)	2145 (20.73)	0.494
Suicidal ideation or intention	1104 (9.48)	128 (9.80)	976 (9.43)	0.707
Anxiety disorder	951 (8.16)	119 (9.11)	832 (8.04)	0.202
Psychosis	441 (3.79)	46 (3.52)	395 (3.82)	0.652
Personality disorder	305 (2.62)	41 (3.14)	264 (2.55)	0.246
Epilepsy	127 (1.09)	18 (1.38)	109 (1.05)	0.356
Schizophrenia	135 (1.16)	17 (1.30)	118 (1.14)	0.707
ADHD b	15 (0.13)	1 (0.08)	14 (0.14)	1.000
Autism	5 (0.04)	0 (0.00)	5 (0.05)	1.000

Note: Numbers may not add exactly because of rounding.
a CVD = Cardiovascular disease
b ADHD = attention deficit hyperactivity disorder

Table 2.
Incidence of cardiovascular disease, by depression duration.

Depression duration	Patients who had incident cardiovascular disease during follow-up (Number of patients with incident CVD/person years at risk)					Incidence per 1000 person-years (95% CI)				
	Overall	Men	Women	65 below	65 +	Overall	Men	Women	65 below	65 and older
All patients	1306/58332	420/14400	886/43931	712/50641	594/7690	22.39 (21.19-23.64)	29.17 (26.44-32.09)	20.17 (18.86-21.54)	14.06 (13.05-15.13)	77.24 (71.16-83.71)
0-1 year	835/44877	286/11327	549/33549	469/39795	366/5082	18.61 (17.37-19.91)	25.25 (22.41-28.35)	16.36 (15.02-17.79)	11.79 (10.74-12.90)	72.02 (64.83-79.79)
2-5 years	221/6954	69/1591	152/5363	121/5816	100/1138	31.78 (27.73-36.26)	43.37 (33.74-54.89)	28.34 (24.02-33.22)	20.80 (17.26-24.86)	87.87 (71.50-106.88)
6 and above years	250/6501	65/1481	185/5020	122/5031	128/1470	38.46 (33.84-43.53)	43.89 (33.87-55.94)	36.86 (31.74-42.57)	24.25 (20.14-28.95)	87.07 (72.64-103.53)

Note: Numbers may not add exactly because of rounding.