Investigating the Bidirectional Association Between Cardiovascular Diseases and Depression

A thesis by

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Abstract

Background: Cardiovascular diseases (CVDs) are the leading cause of disability and mortality globally. Although there has been substantial medical advancement in treating and managing CVDs, surviving CVD patients are at a greater risk of mortality and morbidity. Thus, preventative approaches aiming to identify, manage and control CVD risk factors remain the highest priority.

Depression is a leading cause of disability worldwide, and it has been considered a relevant emergent, non-classical risk factor for the onset and poor prognosis of CVDs. Several systematic reviews have been published on this subject, providing evidence that depression is associated with an increased risk of CVD incidence. However, these reviews were limited by incorporating poor study designs and by focusing predominantly on a single CVD outcome. This previously fragmented investigation masked the overall picture of how strongly depression impacts each CVD subtype.

At the same time, hypertension is one of the biggest risk factors for CVD; hence, the management and control of hypertension is of the utmost importance. Hypertensive patients mainly rely on antihypertensive treatment with a high dosage regimen and/or a combination of several antihypertensive drugs for the long term to control blood pressure and to consequently prevent the development or complication of CVD. Emerging evidence has investigated the effect of antihypertensive drugs in relation to depression onset, though the exact relationship remains unclear. Given that both hypertension and depression are risk factors for CVD, it becomes important that therapeutic agents to control blood pressure not have deleterious effects toward triggering depressive disorders, as both conditions will have a relevant big impact on patient's health particularly those at high CVD risk. **Objectives**: This thesis has two main objectives: (1) updating the evidence of the association between depression and the risk of major subtypes of CVDs and (2) to investigate the association between exposure to antihypertensive drugs and risk of depression incident.

Method: For the first objective, I conducted a systematic review and meta-analyses. Depression in the review referred to depressive symptoms or clinical depression and main outcomes of interest were incidence of fatal/non-fatal

coronary heart diseases (CHD), heart failure (HF) and stroke, each measured as a single endpoint and reported as hazard ratio (HR) and 95% confidence interval (CI). The results for the systematic review were divided into three main results chapters based on the main outcomes (4-6). For the second objective, a secondary analysis of existing data held in the Glasgow Blood Pressure Clinic (GBPC) was conducted. Exposure was antihypertensive drugs which involves the five major classes including calcium channel blocker (CCB), beta-blocker (BB), angiotensin converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB) and thiazide diuretic (TZD). The primary outcome was depression as indicated by the first prescription of antidepressants drug. Main findings of this analysis are presented in chapter 7.

Results: Chapter 4 evaluated the relation between depression and risk of stroke. The meta-analysis included 19 studies enrolling 3,154,290 participants, with an average follow-up of 11.2 years. The pooled estimated risk revealed that baseline depression is associated with a 22% (HR = 1.22, 95% CI, 1.11-1.33) increased risk of developing first-ever stroke, with evidence of substantial statistical heterogeneity between studies (I^2 = 67%). The magnitude of risk presented in this study is more modest than that previously reported in past systematic reviews for stroke outcomes. Sensitivity analyses were carried out to assess for a possible reverse causality (i.e. depression manifested as an acute sickness response to a subclinical stroke). This was achieved by restricting the analysis to four studies that considered a lag period, excluding stroke events occurring during the first years of follow-up. The results showed that depression remains a statistically strong predictor of stroke incidents with a more pronounced effect, and a wider 95% CI was obtained, which might indicate uncertainty (HR = 1.39, 95% CI, 1.11, 1.74). The statistical positive association remained significant after further restricting the analysis to five studies that measured depression over multiple instants over the follow-up period and modelled depression as a time-varying exposure (HR = 1.33, 95% CI, 1.10, 1.59). This finding suggests that elevated lifetime depressive symptoms among adults can be used as a reliable measure to predict future risk of stroke; however, due to the limited number of studies included to derive these findings, the result should be considered with caution and more work is required to confirm this finding. Subgroup analysis was also performed, and the findings showed that depressed elderly participants aged 65

years or above were at a lower risk of developing stroke than depressed participants at a younger age (< 65 years). However, the group difference showed only a borderline significance (p = .5). The results of this analysis may indicate that depression occurring at an early age might have a more devastating effect than late-life depression, though this finding should be considered with caution given the good heart health condition of elderly patients at baseline. Future epidemiological studies should be carried out on a large-scale to identify the clinical characteristics of participants that make them more prone to developing depression at an early age.

Chapter 5 examined the association between depression and incident CHD. The meta-analysis incorporated 23 studies with 33,786299 participants and an average follow-up of 12.4 years. The pooled summary effect showed that the risk of CHD incident increased with depression by 22% (HR= 1.22, 95% CI, 1.13-1.32, p < .000) with evidence of substantial statistical heterogeneity between studies (I^2 = 77%). The estimated risk presented in this study is almost identical to the latest review. This study also found that depression is associated with a 24% higher risk of developing myocardial infarction (HR = 1.24, 95% CI, 1.19, 1.29) with no evidence of statistical heterogeneity between studies (I^2 = 0%). Sensitivity analyses comprising five cohort studies that considered a lag period provided similar risk estimates (HR = 1.22, 95% CI, 1.01, 1.48). Five studies modelled depression as a time varying exposure; a meta-analysis of these studies revealed an increased risk of incident CHD for depression, though a slightly lower magnitude was observed (HR = 1.17, 95% CI, 1.07, 1.28). Subgroup analysis by type of depression measures showed that the effect of clinical depression is more pronounced (HR = 1.26, 95% CI, 1.20, 1.32; I2 = 0%) than depressive symptoms (HR = 1.17, 95% CI, 1.10, 1.25; I2 = 0%) on risk of CHD incidence.

In Chapter 6, I investigated the association between depression and incident HF in a CVD-free population. The meta-analysis was based on only four cohort studies with 2,200,308 participants and an average follow-up of 10.13 years. The main finding revealed that depression was associated with a 17% (HR = 1.17, 95% CI, 1.08, 1.38) increased risk of HF in the absence of CVD events at baseline, with no statistically significant amount of heterogeneity (I^2 = 0%).

The hypothesis of a dose-response relation was also assessed. Overall, this review identified 12 cohort studies that assessed a dose-response relation between depression and CVD outcomes. For stroke outcomes, four studies suggested a dose-response relation, and two did not confirm this finding (chapter 4). For CHD events, four studies showed no evidence of a dose-response relation and four found that depression increased the risk of CHD incident in a dose-response manner (chapter 5). Importantly, there was substantial heterogeneity in terms of how the studies defined 'a dose of depression', which seriously hampered the meta-analysis and drawing of conclusions. Future studies should establish guidance for researchers on the optimal measures of 'a dose of depression' to investigate such a relation.

Chapter 7 covered the investigation of the association between antihypertensive drugs and the risk of incident depression. This was a retrospective cohort study in which I analysed data of hypertensive patients attending the GBPC, providing secondary and tertiary care service, between January 2005 and March 2013. All patients aged between 18 and 80 years who were newly commenced on antihypertensive drugs were included in this cohort. Exposure to ACEI, ARB, BB, CCB, and diuretics was assessed. Patients were prospectively followed up to the outcome, death, or end of the study. Depression as an outcome in this cohort was defined as patients who filled at least two prescriptions of antidepressants during the study period. Two analyses were performed. The first analysis was on patients who were on antihypertensive monotherapy. Eligible patients had no known history of depression and were on an antihypertensive monotherapy of the same drug class within a 12-month window defined as the exposure period. Patients who died or developed the outcome during the exposure period were excluded. The association between antihypertensive drug classes and depression incidence was investigated using Cox proportional hazards models to estimate HR, and patients who received ACEI therapy were set as the reference group. In this analysis, a dose-response relationship was also investigated, whereby the cumulative defined daily dose (cDDD) of antihypertensives during the exposure period was stratified into tertiles and the lowest tertile was set as the reference group. The second analysis was on patients who were either on antihypertensive monotherapy or polytherapy. In this analysis, eligible patients had an exposure period of 6 months preceded by 6 months of no antihypertensive or antidepressant prescription

records. Patients who developed the outcome or died within the six months of the exposure period were excluded. Studied antihypertensive drug classes were additionally included alpha-blocker and centrally acting antihypertensive drugs. CCB and diuretic classes were divided into dihydropyridine CCB and non-dihydropyridine CCB, diuretics, and mineralocorticoids diuretic, correspondingly. Both Cox proportional hazards models and the generalised estimating equation (GEE) were used to investigate the association between antihypertensive drugs and incident depression. The reference group in this analysis was also patients on ACEI therapy. Findings of the monotherapy analysis showed that, among the five major classes of antihypertensive drugs, CCB had the highest risk of developing depression after adjusting for covariates, compared to the ACEI group (HR = 1.39; 95% CI: 1.07, 1.82). Consistence results derived from the polytherapy analysis showed that dihydropyridine CCB was associated with a significantly increased risk of incident depression in comparison to ACEI (HR = 1.38; 95% CI: 1.03, 1.86). The GEE analysis further confirmed this finding (OR = 1.32 95% CI: 1.06, 1.64). The dose-response analysis demonstrated that higher cDDD of ARB was associated with a greater risk of depression, although the association was marginally significant (p = 0.055). **Conclusion:** This thesis provided evidence that depression imposes a similar level of risk across different CVD subtypes. Future epidemiological studies should examine the dynamic aspects of depressive symptoms in relation to CVD and subclinical CVD, whether the risk of CVD is related to a specific subtype of depression, and the role of antidepressant drugs in this association.

The present thesis showed that among population with complicated hypertension, CCB is associated with an increased risk of depression incidence compared to ACEI, supporting findings of previous studies. The risk of developing depression is also linked to ARB, although it might be dose dependent. A well-designed randomised control trial is the optimal study design to validate these findings, and up to that time when a clear association is established, these medications should continue to be used as recommended by the current guidelines for hypertension treatment and CVD prevention.

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Author's Declaration

I declare that this thesis is a presentation of my own research work unless otherwise stated and that it has not been previously submitted to any institution of higher education.

Definitions/Abbreviations

A	Adrenaline
AC	Adenylyl cyclase
ACC/AHA	American College of Cardiology/American Heart Association
ACE	Angiotensin converting enzyme
ACEI	Angiotensin converting enzyme inhibitor
ACTH	Adrenocorticotropic hormone
AD	Alzehimer diseases
AHA	American Heart Association
AMPAR	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
Ang	Angiotensin
APA	Aminopeptidase A
APN	Aminopeptidase N
ARB	Angiotensin receptor blocker
AT	Angiotensin
ATP	Adenosine triphosphate
ßAR	ß-adrenergic receptor
BB	Beta-blocker
BBB	Blood brain barrier
BD	Bipolar depression
BDI	Beck's Depression Inventory scale
BDNF	Brain-derived neurotrophic factor
BMI	Body mass index
BP	Blodd pressure
Ca+2	Calcium ions
cAMP	Cyclic adenosine monophosphate
CCB	Calcium channel blocker
CCI	Charlson Comorbidity Index.
cDDD	Cumulative defined daily dose
CES-D	Centre for Epidemiological Studies Depression scale
CHD	Coronory heart diseases
CI	Confidence interval
CIDI-SF	Composite International Diagnostic Interview- short form
CNS	Central nervous system
COV	Circumventricular organs
CREB	Cyclic adenosine monophosphate response element-binding protein
CRH	Corticotropin-releasing hormone
CRP	C-reactive protein
CVD	Cardiovascular disease
DALYs	Disability-adjusted life-years
DBP	Diastolic blood pressure
DEEX	DEpression and EXhaustion subscale
DHP	Dihydropyridines
DSM	Diagnostic and Statistical Manual of Mental Disorders
eGFR	

ENRICHD	Enhancing Recovery in CHD Patients
EPSC	Excitatory postsynaptic currents
ESH/ESC	European Society Of Hypertension/European Society Of Cardiology
ETC	Excitation-transcription coupling
FDA	Food and Drug Administration
FEM	Fixed-effect model
GDS	Geriatric Depression Scale
GEE	Generalised Estimating Equations
GHQ	General Health Questionnaire
GluA1	Glutamate receptor type 1
GP	General Practitioner
GPCR	G-protein coupled receptor
GWAS	Genome wide association study
HF	Heart failure
HIV	Human Immunodeficiency Virus
HPA	Hypothalamic pituitary adrenal
HR	Hazard ratio
HRV	Heart rate variability
ICD	International Classification of Diseases
IL	Interleukins
IRAP	Insulin responsive aminopeptidase
IS	Ischemic stroke
ISA	Intrinsic sympathomimetic activity
LC	Locus coeruleus
LTP	Long-term potentiation
L-VGCC	L- type voltage-gated calcium channel
MACE	Major adverse cardiac events
MAOI	Monoamine oxidase inhibitor
MDD	Major depressive disorederes
MI	Myocardial infarction
MIND-IT	Myocardial Infarction and Depression–Intervention Trial
MONICA	Multinational MONItoring of trends and determinants in CArdiovascular
MRA	Mineralocorticoid Receptor Antagonist
NA	Noradrenaline
NADPH	Nicotinamide adenine dinucleotide phosphate dehydrogenese
NMDA	N-methyl-d-aspartate
OR	Odd ratio
PCI	Percutaneous coronary intervention
PECOS	Population, Exposure, Comparator, Outcomes, and Stuyd design
PKA	Protein kinase A
PPARδ	Peroxisome proliferator-activated receptors δ
PSD	Post-stroke depression
PSN	Parasympathetic nervous system
PVD	peripheral vascular disease
PVN	Paraventricular nucleus
RAS	Renin–angiotensin system

RCT	Randomised control trial
REM	Random effect model
RR	Risk/relative ratio
SADHART	Sertraline Antidepressant Heart Attack Randomized Trial
SBP	Systolic blood pressure
SCZ	schizophrenia
SFO	Subfornical organ
SIMD	Scottish Index of Multiple Deprivation
SNP	Single nucleotide polymorphism
SNRI	Serotonin-norepinephrine re-uptake inhibitor
SNS	Sympathetic nervous system
SRS	Self-reported Scale
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant
TIA	Trainset ischemic attack
TNF	Tumour necrosis factor
TrkB	Tropomyosin-Related Kinase B Receptors
TZD	Thiazide diuretics
UK	United Kingdom
US	United States
VGCC	Voltage-gated calcium channel
WHO	World health organisation

1 Introduction

1.1 Depression and Cardiovascular diseases (CVD)

1.1.1 CVD definition and prevalence

According to the World health organsiation (WHO), CVD is a general term for a group of diseases affecting the heart and blood vessels, which refers to coronary heart diseases (CHD), stroke and trainset ischemic attack (TIA), heart failure (HF), peripheral vascular disease (PVD), rheumatic heart diseases, congenital heart diseases and deep vein thrombosis and pulmonary embolism (WHO, 2017a)

CVD is the leading cause of death worldwide, accounting for more than 17 million deaths in 2016, which corresponded to 31% of all global deaths (WHO, 2017a). This figure is expected to increase to more than 23.6 million by 2030 (AHA, 2015), meaning CVDs are projected to remain the single largest cause of death worldwide. Among the different types of CVD, CHD and all forms of stroke are the main cause of death, and one-third of these deaths occur prematurely in people under the age of 70. The risk of CVD is not limited to mortality; it can also cause severe disabilities, particularly among patients who survived a stroke or a myocardial infarction (MI) event.

1.1.2 Depression definition and prevalence

The definition of depression relies on identifying several symptoms that form a syndrome causing functional impairment (Malhi and Mann, 2018). Key symptoms that are relatively specific to depression include anhedonia and depressed mood. Other symptoms involve cognitive and somatic symptoms (Figure 1-1). However, it should be noted that, none of the symptoms are pathognomonic of depression, and do feature in other psychiatric and medical illnesses. For example, somatic symptoms including fatigue, appetite disturbance and sleep disturbance are very common in other medical illness. The two main classificatory diagnostic systems used to diagnose clinical depression are the International Classification of Diseases (ICD) and the Diagnostic and Statistical Manual of Mental Disorders (DSM), but the DSM is widely used for research. In order to qualify as major depressive disorder (MDD) based on the DSM, an individual should be presented with five or more

depressive symptoms including anhedonia and depressed mood, for nearly every day during a 2-week period. Depressive symptoms that do not meet the above criteria often regarded as subthreshold depressive symptoms, which could serve as early indicator of a major depressive episode. A depressive episode can be also described in a greater depth using a specifier which defines the pattern of the illness (e.g. a single or a recurrent episode), the severity (e.g. mild, moderate or severe), time of onset (e.g. early, late life or postpartum) and whether it has remitted.

Based on the spectrum view of mood disorders, there is no distinct qualitative differences between MDD and mild episode of sadness. Instead, they lie along a continuum of depressive states. The only exception is melancholic depression, which does seem to differ qualitatively from normal sadness in some respects.

A recent epidemiological survey stated that more than 322 million people of all ages are living with depression, accounting for 4.4% of the global population (WHO, 2017b). Between 2005 and 2015, there was an 18.4% increase in the number of people living with depression, and by 2015, depressive disorders were the single largest contributor to nonfatal health loss globally (GBD 2015 Disease and Injury Incidence and Prevalence, 2016).

The burden of depressive disorder extends far beyond the disorder. The WHO describes depression as a leading cause of disability worldwide and the major contributor to the overall global burden of diseases. Depression can become a serious health condition threatening patients' life and quality of life. Evidence shows that depression increases risk of all-cause and specific-cause mortality, traumatic death and suicide in the general population, especially with long-lasting moderate to severe symptoms (Melhem et al., 2019). Cardiovascular mortality is the most common cause-specific mortality in depressed individuals after an initial cardiac or neurological event; this risk also relates to the severity of the depressive episode (Bartoli et al., 2018, May et al., 2017).

1.1.3 **Identification of depression**

Accurate identification of depression is a crucial step for providing effective treatment for depressed patients. It has been recognised that general

practitioners (GPs) fail to make accurate diagnoses of depression. Studies have shown that about 50% of primary care cases of depression go undetected and therefore untreated (National Collaborating Centre for Mental Health, 2010b). However, it is more likely that mild to moderate symptoms go underdiagnosed compared to severe or clinically important symptoms (National Collaborating Centre for Mental Health, 2010b). Diagnosing depression is even more complicated in depressed patients suffering from other physical health conditions. One study reported a detection rate by GPs of 95% for patients with depression alone, but a much lower rate of 23% was reported for patients exhibiting depression alongside other physical health problems (Bridges and Goldberg, 1985). This low rate is mainly because it is difficult to distinguish somatic symptoms related to depression from those related to the physical health problem. Depressive symptoms can be categorised into somatic symptoms, such as fatigue, appetite disturbance and sleep disturbance, and non-somatic symptoms, which include affective and cognitive impairments (Figure 1-1). Previous studies have therefore suggested a simplified method of diagnosis criteria using only non-somatic symptoms to identify depression in patients with a physical condition to overcome overlapping symptoms (National Collaborating Centre for Mental Health, 2010a).

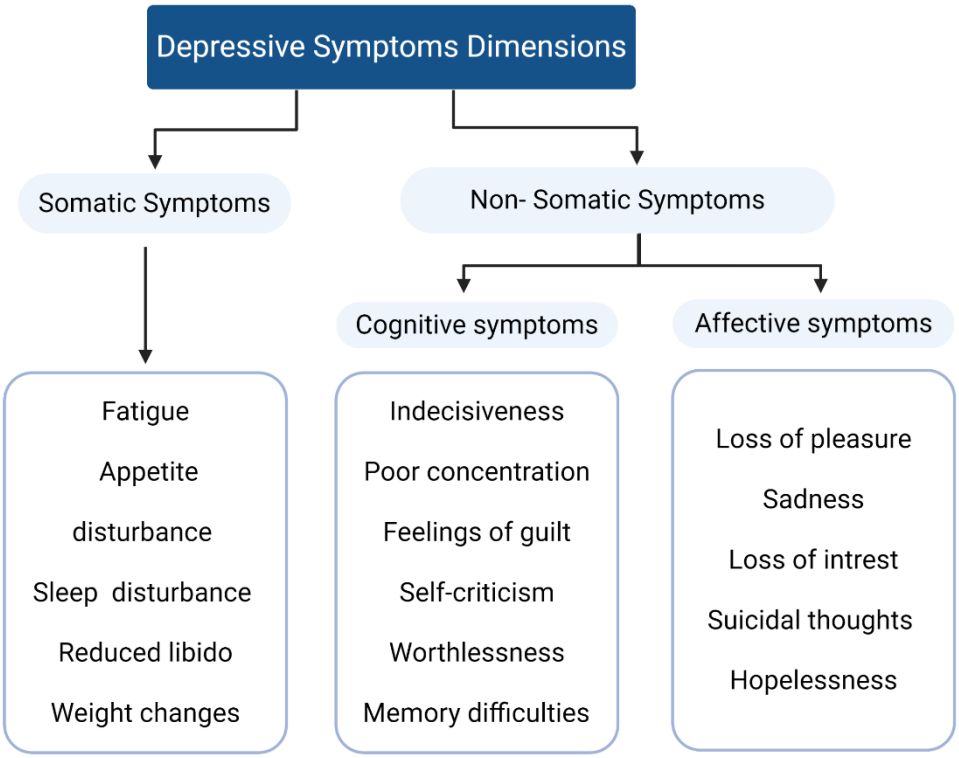

Figure 1-1 Depressive symptoms dimensions
Information modifie from (O'Shea et al., 2018)

Overall, evidence from the literature regarding depression and CVD can be summarised in three points: (1) depression and CVD are highly comorbid (Khandaker et al., 2019); (2) depression can increase CVD incidence (and vice versa), either directly or indirectly, by increasing the incidence of CVD classical risk factors, such as hypertension , obesity and diabetes; and (3) depression is a potential predictor of poor health prognosis in CVD patients.

1.1.4 Depression and CVD as comorbid diseases

1.1.4.1 Depression in CVD patients

Patients with established CVD are at a higher risk of developing depression compared to the general population, and depression prevalence in CVD patients varies based on the type and severity of the CVD. Studies that have investigated the prevalence of depression in CHD patients reported considerably varied estimates. For example, Ziegelstein (2001) showed that approximately 15% to 20% of CHD patients have depression and up to two-thirds of MI patients experienced depressive symptoms during the index admission. Another study reported that up to 40% of CHD patients met the diagnostic criteria of MDD (Huffman et al., 2013). Among patients with PVD, the prevalence of depression was found to be up to 48% (Brostow et al., 2017). Regarding HF, data from two large meta-analyses showed an approximate prevalence of depression of 20%-30%, and this rate is similar across different HF aetiologies (Sbolli et al., 2020). Epidemiological studies investigating the prevalence of post-stroke depression have reported widely variable estimates ranging from 10% to 81%, though the occurrence of depression in stroke patients is more likely to relate to the level of functional disability after the stroke event (Vojtikiv-Samoilovska and Arsovska, 2018).

1.1.4.2 CVD in depressed patients

Epidemiological and observational studies investigating the prevalence of CVD in depressed patients reported varied estimates of prevalence. For example, the results from the Medical Outcomes Study in a sample of outpatients with MDD or depressive symptoms showed that 5% of these patients were diagnosed with CHD and 4% reported having angina (Wells et al., 1989, Air et al., 2017). Another study reported a prevalence of 12% for CHD and 5% for HF in depressed patients (Lyness et al., 1993). Higher prevalence estimates were reported in a case-control study,

which found that 46.1% of patients suffering from recurrent depression also had CVD, compared with 13.9% in the control group (Topic et al., 2013).

1.1.5 **Depression and risk of CVD incidence**

The association between depression and CVD has long been recognised. The impact of mental health on the pathogenesis of CVDs was first described by William Harvey in 1628. Harvey proposed that mental distress can negatively affect the heart and impair its function (Rumsfeld and Ho, 2005). However, this potential association was largely ignored until the 1930s, when an epidemiological study found that institutionalised psychiatric patients with melancholia had a mortality rate eight times higher than the general population and that heart diseases accounted for almost 40% of these deaths (Malzberg, 1937). Further support for this suggestion came from Dreyfuss and colleagues in the late 1960s. The authors found that depressed patients had a six times higher risk of MI compared to patients with other psychiatric diseases and, as depressive symptoms usually preceded the MI event, they concluded that depression may cause MI (Dreyfuss et al., 1969). Despite this early evidence, the interest in the role of depression in CVD only surged in the late 1980s, and since then, hundreds of prospective studies and reviews have been published.

However, the inconsistent findings of prospective studies (Almas et al., 2015, Kyrou et al., 2017, van Marwijk et al., 2015, Penninx et al., 1998, Vinkers et al., 2004) highlighted the need for an objective meta-analysis of this literature. Between 2002 and 2016, 10 meta-analyses were published, all of which identified depression as an independent risk factor for incidence of CVD (Van der Kooy et al., 2007) and CVD subtypes, including CHD (Rugulies, 2002, Wulsin and Singal, 2003, Nicholson et al., 2006, Gan et al., 2014, Wu and Kling, 2016) and strokes (Pan et al., 2011b, Dong et al., 2012, Barlinn et al., 2015, Li et al., 2015a). As illustrated in Table 1-1**Error! Reference source not found.**, the quantified risk of depression varied considerably across the studies, particularly those focused on CHD outcomes, which ranged from 20% to 90%. Meta-analysis of studies that assessed the risk of depression in relation to strokes reported an approximately stable risk estimated in the range of 40%-50% (Barlinn et al., 2015, Li et al., 2015a, Pan et al., 2011b, Van der Kooy et al., 2007), though one reported a lower risk (34%) (Dong et al., 2012). The meta-analysis conducted by Van der Kooy et al.

(2007) showed that depression was associated with a 57% increased risk of CVD in initially healthy individuals. A recent prospective cohort study reported a more modest effect of depression on overall CVD incident. Rajan et al. (2020) enrolled 145,862 participants from 21 countries with different levels of economic development to identify the association between depression and incidences of CVD and all-cause mortality. Over a median follow-up of 9.3 years, they found that participants who had experienced at least four depressive symptoms before study entry had a 14% increased risk for a future CVD event (HR, 1.14; 95% CI 1.05-1.24) compared to participants who had not. Their findings also showed that depression is associated with an increased risk of future MI (HR = 1.23; 95% CI 1.10-1.37) but not stroke (HR = 1.05, 95% CI 0.91-1.21) or HF (HR = 1.09, 95% CI 0.86-1.39).

Depression may confer different degrees of risk for each CVD subtype. However, based on the previously conducted meta-analysis, the magnitude of risk for each CVD subtype cannot be determined with confidence for several reasons. First, early studies did not adjust properly for potential confounders, especially those that were proposed to be in the causal pathways between depression and CVD, which may have led to an overestimation of the estimated risk. This problem was first identified by Nicholson et al. (2006), who conducted a meta-analysis to estimate the risk between depression and CHD. Their findings showed that about 50% of the eligible studies did not adjust for potential confounders. After stratifying the analysis based on the degree of confounder adjustment, they found a 12% lower risk of CHD in an adjusted risk estimate (RR = 1.90, 95% CI 1.49-2.42) compared with an unadjusted risk estimate (RR = 2.08, 95% CI 1.69–2.55). Another possible reason is that the majority of the previously conducted meta-analyses have not focused on CVD-free participants as the target population. Of the 10 meta-analyses, only two considered excluding studies that enrolled patients with a previous history of CHD or stroke at baseline. Evidence shows that stroke patients are at a high risk of having another major vascular event, such as CHD (Amarenco and Steg, 2008). Observational studies and RCT suggest that the risk of having a second stroke decreases within the first two years following the first stroke event, whereas the risk of MI increases continuously over time (Amarenco and Steg, 2008, Vickrey et al., 2002). Likewise, CHD patients are at a higher risk of developing stroke than the general population (Matthews, 2006). Based on this

evidence, it is plausible to expect that the results from the majority of previous meta-analyses may be driven by the pre-existence of clinically apparent CVD, and it remains unclear whether depression can be considered a pre-morbid risk factor for stroke and/or CHD, which may also affect the magnitude of the true association between depression and CVD.

Table 1-1 Depression as a risk factor for incident CVD

Meta-analysis	Search period	Type of included studies	Number of studies	Outcome	Excluding CVD at baseline (other than the outcome of interest)	HR or RR (95% CI) of CVD
(Rugulies, 2002)	1887-2000	Prospective cohort studies	11	CHD	No	1.64 (1.29-2.08)
(Wulsin and Singal, 2003)	1966-2000	Prospective cohort studies	10	CHD	**Yes**	1.64 (1.41-1.90)
(Nicholson et al., 2006)	1966-2003	Prospective cohort studies	11⁺	CHD	No	1.90 (1.49-2.42)
(Van der Kooy et al., 2007)	1966-2005	Prospective cohort and case-control studies	16	CHD	No	1.48 (1.29, 1.69)
			16*	CVD	**Yes**	1.57 (1.36-1.81)
			10	Stroke	No	1.43 (1.17-1.75)
(Pan et al., 2011b)	Up to 2011	Prospective cohort studies	24‡	Stroke	No	1.44 (1.26–1.65)
(Dong et al., 2012)	Up to 2010	Prospective cohort studies	17	Stroke	No	1.34 (1.17-1.52)
(Gan et al., 2014)	Up to 2014	Prospective cohort studies	30	CHD	No	1.30 (1.22-1.40)
(Barlinn et al., 2015)	Up to 2014	Prospective cohort studies	15*	Stroke	**Yes**	1.43 (1.19-1.72)
(Li et al., 2015a)	Up to 2014	Prospective cohort studies	30‡	Stroke	No	1.48 (1.30–1.67)
(Wu and Kling, 2016)	1966-2015	Prospective cohort studies	19	CHD	No	1.22 (1.13-1.32)

CHD, coronary heart disease. CVD, cardiovascular disease. HR, hazard ratio. RR, relative risk. ⁺studies with adjusted HR. *Included only those studies of participants without CVD at baseline. ‡ Excluded baseline stroke.

1.1.6 **Common hypothesised pathways linking depression to CVD**

The mechanisms by which depression leads to CVD are most widely investigated in relation to CHD, but they are strikingly similar across other CVD subtypes **Figure 1-2** summarises the most common pathways proposed to explain the depression-CVD relationship, which include neurohormonal and autonomic dysfunction, dysregulation of the immune system, coagulation abnormalities and vascular endothelial dysfunction, and behavioural mechanisms..

Neurohormonal and autonomic dysfunction caused by depression are associated with an overactivation of the hypothalamic pituitary adrenal (HPA) axis and sympathetic nervous system (SNS)(Huffman et al., 2013). Hyperactivation of the HPA axis triggers the hypersecretion of the adrenocorticotropic hormone (ACTH) and the subsequent elevation of cortisol and catecholamine plasma levels. Chronic elevated levels of cortisol or hypercortisolism increase the risk of the development and progression of metabolic syndrome which ultimately cause CVD. Hypercortisolism also mediates a sustained increase in the immune response mechanism. Further, it has been suggested that depression is associated with enhancing SNS activity, creating an autonomic imbalance between the SNS and the parasympathetic nervous system (PSN) activity. The result is an increase in heart rate, a vasoconstriction of blood vessels and event

ually high blood pressure (BP). Additionally, hyperactivation of the SNS causes a reduction in baroreflex sensitivity response and heart rate variability (HRV), resulting in cardiac autonomic dysfunction and arrhythmia, which have a substantial role in HF pathology (Shi et al., 2017).

Depression promotes increased levels of proinflammatory cytokines and reduced levels of anti-inflammatory cytokines in the immune mechanism, causing an insufficient control of the immune response (Baune et al., 2012). Proinflammatory cytokines, including interleukins (IL), such as IL-1, IL-2, IL-6, tumour necrosis factor (TNF-α) and C-reactive protein (CRP), have been linked to CVD. Prolonged activation of inflammatory mediators leads to oxidative stress and endothelial damage, which may accelerate and amplify the progression of atherosclerosis, coagulation and thrombus formation and eventually CVD incidence.

Evidence from genetic studies showed that pleiotropic genes are likely to be shared with depression and CVD further expanded the possible biological pathways linking these two diseases. Amare et al. (2017) identified 24 overlapping genes between mood disorders and cardiometabolic disorders and linked them to 10 molecular pathways encoded by these genes.

While behavioural mechanisms can play an important role in mediating the CVD risk associated with depression, they do not on their own account for the link between the two disease entities (Stapelberg et al., 2011). Depressed patients are likely to adopt and maintain poor health behaviours, such as poor diet, smoking, low physical activity and poor medication adherence, placing them at a higher risk of developing metabolic syndrome and CVD (Stapelberg et al., 2011).

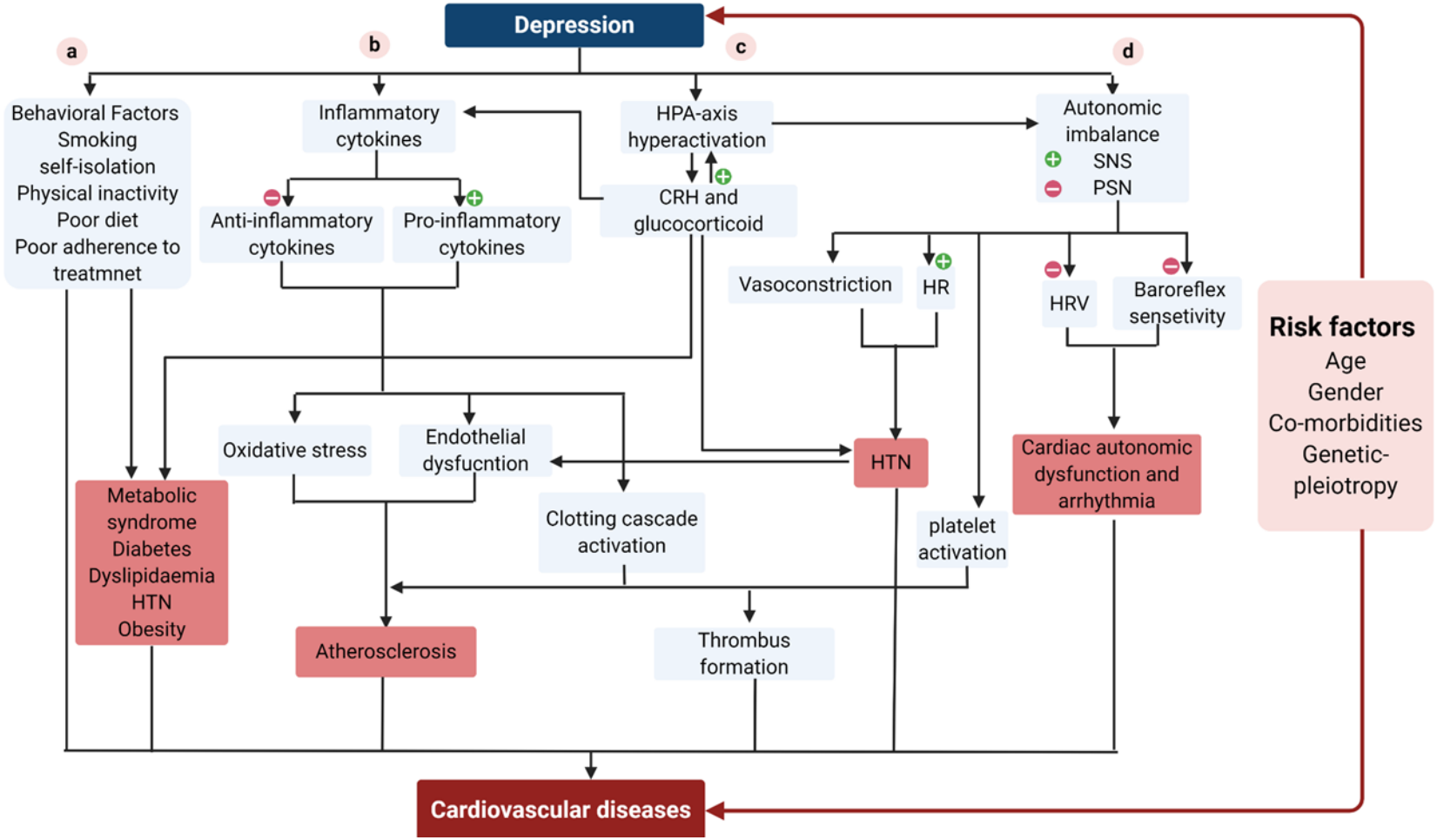

Figure 1-2 Pathways linking depression with CVD
Figure modified from (Baune et al., 2012, Hare et al., 2014, Stapelberg et al., 2011). a) Behavioral mechanism. b) Inflammatory mechanism. c) and d) Autonomic dysfunction. Abbreviation: CRH, Corticotrophin releasing hormone; HTN, hypertension; HPA-axis; hypothalamic-pituitary-adrenal axis; HR, heart rate; HRV, heart rate variability; PSN, Parasympathetic nervous system, SNS, sympathetic nervous system.

1.1.7 **Antidepressants medication and risk of CVD**

Antidepressants is one of the first-line treatment for depression and it should be considered for treating patients showing moderate to severe depressive symptoms or those patients with mild symptoms but with a history of moderate or severe depression.

When discussing the role of antidepressant medications, particularly in the context of CVD, it is important to determine whether (1) antidepressants are associated with an increased or reduced risk of CVD incidence in healthy individuals and (2) treating depressive symptoms with antidepressant medication can reduce the risk of poor health outcomes in CVD patients with depression.

The major classes of antidepressants are tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine re-uptake inhibitors (SNRIs) and monoamine oxidase inhibitors (MAOIs). Of these classes, TCAs and MAOIs have fallen out of favour in clinical practice and are rather reserved for treating resistant depression cases mainly due to their side effects profile and safety concerns. TCA is known to cause cardiotoxicity through affecting normal cardiac contractility and HRV, which are linked to worsening CHD and sudden cardiac death. By contrast, SSRIs have shown to have a positive effect on specific pathophysiological disturbances whereby depression increases the risk of CVD. For example, SSRIs may inhibit platelet aggregation (Halperin and Reber, 2007) which in turn reduces atherosclerosis risk and thrombotic events and eventually decreases the risk of CVD incidences. Several meta-analyses and observational studies have evaluated the association between antidepressant medication and CVD in healthy depressed patients. Hamer et al. (2011) conducted a prospective cohort study of 14,784 adults with no known history of CVD using data from the Scottish Health Survey. They showed that TCAs were associated with a 35% increased risk of CVD but not CHD incidences, but SSRIs were not associated with a greater CVD risk. These findings were confirmed by a later meta-analysis of 16 observational studies enrolling CHD-free patients (Oh et al., 2014). The results from the study provided no evidence that TCAs and SSRIs are associated with an increased risk of CHD incidence in this population. More recently, Almuwaqqat et al. (2019) proposed that SSRIs are not superior to other antidepressant medications in reducing the risk of developing CVD in depressed

patients with no previous CVD. The exact relation between different antidepressants drug classes and CVD incident remain to be established.

The question of whether poor cardiac prognosis can be improved in depressed patients by treating depressive symptoms remains controversial. In the literature, the following three major randomised control trials (RCTs) attempted to answer this question: the Enhancing Recovery in CHD Patients (ENRICHD) trial (Berkman et al., 2003), the Myocardial Infarction and Depression–Intervention Trial (MIND-IT) (van Melle et al., 2007) and the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART)(Glassman et al., 2002b). In brief, the trials failed to detect any significant differences in cardiac outcomes between the antidepressant and control groups in cardiac patients. However, in a post-hoc subgroup analysis, findings from the ENRICHD trial demonstrated that patients who did not respond to antidepressant treatment were at higher risk for late mortality (over 29 months follow-up) than patients who responded, but that was only observed within the active treatment arm (Carney et al., 2004). A post-hoc subgroup analysis from the MIND-IT trial reached the same conclusion regrading poor prognosis in non-respondent depressed patients in relation to cardiac outcomes (either new cardiac event or cardiac mortality) (de Jonge et al., 2007). Similarly, a supplementary report from the SADHART trial showed that the failure to improve depression within the first six months after a cardiac event, in both the intervention and control arms, was significantly associated with all-cause mortality over 6.7 years of follow-up (Glassman et al., 2009). More encouraging findings had reported by recent studies. Kim et al. (2018), conducted an RCT among 300 patients with recent acute coronary syndrome and depression. Patients were assigned for either flexible doses of escitalopram or a placebo for 24 months and followed up for a median of 8.1 years. The primary outcome was major adverse cardiac events (MACE). For the first time, the findings from this RCT showed that escitalopram significantly reduced the risk of MACE (HR= 0.68, 95% CI 0.49–0.96, P-value= 0.03) over the follow-up duration; however, of the four secondary endpoints, the difference was significant only for the MI incidence (HR= 0.54; 95% CI, 0.27-0.96; P = 0.04). With respect to the association between depression remission status and MACE incident, the study investigators further emphasised the importance of improving depressive symptoms to achieve better

cardiac outcomes; they showed that the remitted group was at a significantly lower risk of developing MACE than the non-remitted group (Kim et al., 2018).

1.1.8 Cardiovascular medication and risk of depression: an overview

A host of cardiovascular medication have been historically linked to neuropsychiatric disorders such as anxiety, mood syndromes, psychosis and cognitive disturbances. Some drugs had suggested to induce neuropsychiatric symptoms, while others may have anti-manic or anti-depressants activity (Huffman and Stern, 2007). In the following section I briefly summarised evidence of the most common cardiac medications suggested to have an effect on depression. These medications involve, antihypertensive drugs, lipid lowering agents, antiplatelets and cardiac glycoside.

Perhaps the most extensively studied cardiovascular medications in relation to depression were the antihypertensive medications. There has been a long debate about the capacity of antihypertensive medications to produce depression as a side effect and more recently whether they can be repurposed as a new therapeutic agent to treat depression (Shaw et al., 2019). The relationship between the five major classes of antihypertensive drug including calcium channel blocker (CCB), beta-blocker (BB), renin angiotensin system (RAS) antagonist, thiazide diuretics (TZD) and risk for depression are described in section 1.2.5. Other antihypertensive agent that has been linked to depression is reserpine. Reserpine is an alkaloid extract from the root of *Rauwolfia serpentine*. In 1931, it was first described in Indian literature as an herbal remedy for insanity and hypertension, though it was not introduced to modern medicine until the mid-1940s (Mashour et al., 1998). Between 1960s and 1990s several RCTs had conducted in western countries and consistently reported that reserpine is a powerful BP lowering agent when combined with other antihypertensive treatment including diuretics or diuretics and vasodilators (Zhu et al., 2019). Despite its effectiveness in lowering BP, the clinical uses of reserpine have been declined dramatically due to safety concerns. It has been linked to severe depression that resulted in suicide and hospital admission and other serious health problem such as breast cancer and gastric bleeding (Lavorato and Patten, 1999, Slim et al., 2011).

Digoxin is a cardiac glycoside derived from the foxglove plant, Digitalis lanata. It has been used in the treatment of HF and as a rate control agent for atrial fibrillation and atrial flutter. In general, mental adverse effect of digoxin are very uncommon or rare (Celano et al., 2011). Few case reports and small trials had suggested a link between digoxin and depression, however, larger prospective trials have not supported a strong association between digoxin and the development of depression (Huffman and Stern, 2007). As inflammation is one of the potential mechanisms that has been implicated in depression etiology, agents with anti-inflammatory properties have been proposed as a treatment for depression. For example, statins are lipid lowering agents that have been used to reduce the risk of CVD. Meanwhile, they were suggested to have a possible therapeutic benefit in depression as they possess immunomodulatory, anti-inflammatory, and antioxidant properties (Kim et al., 2019b). Several studies had evaluated the efficacy of statin either as an adjunctive therapy or as a primary therapy for depression, however, findings are largely contradicting (Agustini et al., 2019, Dave et al., 2018, Kessing et al., 2019, Köhler-Forsberg et al., 2019, Mansi et al., 2013, Parsaik et al., 2014, Salagre et al., 2016). Another example is aspirin, also known as acetylsalicylic acid, which belongs to the non-steroidal anti-inflammatory drugs. Aspirin is an antiplatelet agent that prevents thrombus formation and therefore it has been used in the prevention and treatment of CVD. At low doses aspirin inhibits cyclooxygenase-1 enzyme whereby produced neuroprotective effect. A small open RCT with 24 non -responder depressed patients showed that adding aspirin to SSRI for 4 weeks led to rapid and sustained response of over 50% of the patients (Mendlewicz et al., 2006). Subsequent epidemiological and RCT studies have produced inconsistent results when evaluated aspirin as a primary therapeutic agent for depression (Berk et al., 2020, Glaus et al., 2015, Kessing et al., 2019).

1.2 Depression and hypertension

1.2.1 Hypertension

Hypertension, also known as high BP, is a condition in which the blood exerted a high force against the artery walls of the systematic circulation. The overall BP is maintained by cardiac output and peripheral vascular resistance. Cardiac output is a function of heart rate and stroke volume, while peripheral vascular resistance

is a function of the viscosity of blood and rigidity of the blood vessel walls. The determinants of BP are regulated by several physiological mechanisms, including cardiac contractility, homeostasis of extracellular fluids and tone of vascular musculature.

BP consists of two determines: systolic pressure (SBP), which represents the maximum pressure during contraction of the ventricles, and diastolic pressure (DBP), which is the minimum pressure recorded just prior to the next contraction. There is a cut-off BP value that has been universally accepted to facilitate diagnostic approach and clinical decisions about treatment initiation. As a general guide, BP is considered to be normal or optimal when SBP is 80-120 mmHg and DBP is 60-90 mmHg. Conventionally, hypertension is diagnosed when a clinic SBP is 140 mmHg or higher and/or DBP is 90 mmHg or higher. However, recently, there have been some differences in defining and classifying hypertension stages between guidelines. For example, according to the European Society of Cardiology (ESC)/European Society of Hypertension (ESH) guidelines, hypertension is a BP of (SBP/DBP) ≥140/90 mmHg (Williams et al., 2018), while the American College of Cardiology/American Heart Association (ACC/AHA) guidelines changed the definition of hypertension to a lower BP (SBP/DBP) ≥130/80 mmHg (Whelton et al., 2018) **(Table 1-2**). In terms of the classifications, the ESH/ESC guideline continues to classify BP ≥140/90 as stage 1 hypertension (140-159/90-99 mm Hg), while the ACC/AHA guideline classifies this as stage 2 hypertension. On the other hand, the ACC/AHA guideline considers a BP of ≥130/80 (130-139/85-89 mm Hg) mmHg as stage 1 hypertension and the ESH/ESC considers it a high normal BP.

1.2.2 **Prevalence and global burden of hypertension**

According to an estimation from a multinational statistical survey derived from a 135 population-based study enrolling 968,419 adults from 90 countries, the global age-standardised prevalence of hypertension was 31.1% in 2010 (Mills et al., 2016). This estimate of age-standardised hypertension prevalence was almost consistent with sex (31.9% in men and 30.1% in women). However, the study showed that large global disparities exist in the prevalence of hypertension depending on economic development (Mills et al., 2016). The most recent report from the Global burden diseases (GBD) had updated estimates of SBP changes from 1990 to 2015 using data from 154 countries, including 8.7 million individuals (Forouzanfar et

al., 2017). The GBD demonstrated that the prevalence of high SBP, defined as ≥140 mmHg, increased by 3.2% from 17.3% in 1990 to 20.5% in 2015.

Hypertension is known as the strongest risk factor for all CVD acquired during life. In 2015, Forouzanfar and colleagues estimated that the number of deaths attributed to elevated SBP (≥ 140 mmHg) was 7.8 million, which represents 14.0% of all deaths. The risk was not limited to high levels of SBP, as the number of deaths linked to lower levels of SBP ≥110−115 mmHg was 10.7 million (19.2% of all deaths) (Forouzanfar et al., 2017). The authors also showed that at all levels of SBP, CHD is the largest contributor to SBP-related deaths, followed by ischemic stroke and haemorrhagic stroke (Forouzanfar et al., 2017). Hypertension is also associated with an increased risk of diseases other than CVD, such as kidney disease, diabetes and dementia. A systematic review and meta-analysis of six prospective cohort studies showed that prehypertensive patients had a 1.5X increased risk of end-stage renal disease compared to normotensive patients (Huang et al., 2014). The risk carried by high BP is not limited to hypertensive or prehypertensive patients. Evidence showed that the risk of CVD increased exponentially as BP increase even within the normal range of BP, suggesting that SBP may not need to exceed the clinic BP threshold to be considered a risk factor for CVD (Whelton et al., 2020).

Table 1-2 Definitions of BP categories according to the American and European guidelines

Blood pressure category	ACC/AHA (SBP/DBP) mm Hg	ESC/ESH (SBP/DBP) mm Hg
Normal range of BP	<120/80	<120/80
Elevated BP	120-129/<80	130-139/85-89
Hypertension stage 1	130-139/80-89	140-159/90-99
Hypertension stage 2	≥140/90	160-179/100-109
Hypertension crises	≥180/120	≥180/110

Abbreviations: AHA/ACC, American College of Cardiology/ American Heart Association; ESH/ESC, European Society of Hypertension/ European Society of Cardiology; SBP, systolic blood pressure; DBP, diastolic blood pressure.

As co-existing conditions, depression and hypertension have a far more detrimental effect on health than as individual conditions. As previously mentioned, both conditions are associated with an increased risk of CVD and mortality. Moreover, studies suggest that the impact of depression as a comorbid condition in hypertensive patients may have a major bearing upon physical functioning, quality of life, treatment compliance and healthcare utilisation (Wiehe et al., 2006).

1.2.3 **Hypertension and risk of depression**

Depression is highly prevalent among hypertensive patients. Li et al. (2015b) conducted a meta-analysis of 41 studies comprising 30,796 participants and reported that approximately 27% of hypertensive patients had depressive symptoms. More recent studies conducted in low- and middle-income countries reported an even higher prevalence of depression among hypertensive patients, ranging from 25%-40% (Mahmood et al., 2017, Valladares-Garrido et al., 2020, Gebre et al., 2020).

Overall, studies that have investigated whether hypertension is associated with an increased risk of depression are limited, and most have examined hypertension in relation to late-life depression. Two systematic reviews have been conducted in this regard with consistent findings. First, Valkanova and Ebmeier (2013) conducted a meta-analysis of 14 studies, including cross-sectional and prospective studies, and found no association between hypertension and depression (OR= 1.14; 95% CI 94–1.40; P-value =0.19). Second, Long et al. (2015) conducted a meta-analysis of five prospective cohort studies and found no evidence of an association between hypertension and depression incidence (RR = 1.16, 95% CI 0.91, 1.42). However, there is also evidence suggesting that low BP could lead to depression (Licht et al., 2009, Hildrum et al., 2007, Ng et al., 2010, Kim et al., 2010)

Some evidence has linked the increased prevalence of depression in hypertensive patients to the perception of being a chronically ill patient. They proposed that elevated BP levels may have no direct effect on depression and that depressive symptoms may be a consequence of the psychological effect accompanied by a chronic illness (Hamer et al., 2010, Villarreal-Zegarra and Bernabe-Ortiz, 2020).

1.2.4 Depression and risk of hypertension

The hypothesis that depression may increase the risk of hypertension has been studied for more than a century. In 1898, Maurice Craig observed that during a depressive episode, BP was always elevated and returned to normal after remission (Friedman and Bennet, 1977). Since that time, several clinical studies have attempted to establish the nature of the relationship between these two diseases. So far, only one meta-analysis of this literature has been published (Meng et al., 2012), which comprised nine prospective studies; the main finding showed that depressed patients had a 42% (RR= 1.42; 95%CI 1.09 ,1.86, p = 0.009) higher risk of developing hypertension than non-depressed patients.

1.2.5 Antihypertensive drug class and risk of depression

The following section closely describes the relationship between the major five classes of antihypertensive drugs, including CCBs, BBs, RAS antagonists, TZDs and risk for depression. Table 1-6 summarises epidemiological studies that had investigated the association between different classes of antihypertensive drugs and depression.

1.2.6 CCBs and risk of depression

1.2.6.1 Calcium channels

Calcium channels are present in most cell types of mammalian bodies and have critical functions in various cellular processes. There are several types of calcium channels regulating calcium ions (Ca^{+2}) influx through cell membranes, including voltage-gated channels, ligand-gated channels and/or sodium (Na^{+})/Ca^{+2} exchanger pumps. Since most of the available CCBs act on the voltage-gated calcium channel (VGCC) to produce their therapeutic effect in cardiovascular tissue, the next section focuses on the molecular structure of VGCC, particularly the L-type Ca^{+2} channel, different subtypes and their distinct function in various tissues.

VGCCs are transmembrane ion channel proteins that act as key signal transducers of electrical excitability, transforming electrical signalling derived from membrane action potential to an intracellular Ca^{+2} transient (Catterall, 2011).

Ca^{+2} entering the cell serves as a second messenger initiating different cellular events depending on the type and location of the VGCC. VGCCs are grouped into three families – Ca_V1, Ca_V2 and Ca_V3 – which form 10 isoforms; each has a distinct physiological and pharmacological effect. Table 1-3 summarises information on each member of the VGCC families. Among the three channel families, the L-type VGCC (L-VGCC) channel possess a crucial role in cardiovascular tissues, making them a specific target for therapeutic agents, namely CCB, for the treatment of CVDs. L-VGCC is composed of the heteromultimeric protein complex consisting of a central pore forming α1 and the auxiliary channel α2/δ, β and, in some tissues, γ subunits, which bind tightly but non-covalently to α1. This Ca^{+2} channel family consists of four isomers, including CaV1.1, CaV1.2 , CaV1.3, and CaV1.4. CaV1.2 and CaV1.3 isomers are localised in various tissues and are often expressed in the same cells, including the cardiac muscle, smooth muscles, neurons and endocrine, but their contribution to the L-type current varies depending on the region. In cardiac myocytes, CaV1.2 is more predominant and Ca^{+2} influx through this channel initiates excitation-contraction coupling. By contrast, the CaV1.3 channel is more predominant in the sinoatrial node, where it is required for a regular cardiac pacemaking function in atrioventricular node (Zamponi et al., 2015). Unlike CaV1.2 and CaV1.3, the tissue expression of CaV1.1 and CaV1.4 is limited to certain tissues. skeletal muscle and retina (Zamponi et al., 2015).

1.2.6.2 **Molecular role of L-VGCC in depression**

The critical role of Ca^{+2} signalling pathways through L-VGCC channels in the brain contributing to neurodevelopmental disorders, depression and other neuropsychiatric diseases has been established by several lines of evidence from both animal models and human studies. Among the four isoforms of L-VGCC, CaV1.2 and CaV1.3 were the strong candidates contributing to these pathological conditions. In the brain, CaV1.2 and CaV1.3 are much more complex than those presenting in the cardiac tissue in terms of structure considering the additional diversity of the auxiliary subunits and the fact that all α 1 subunits seem to be capable of assembling with all β and α 2 δ isoforms (Pichler et al., 1997, Schlick et al., 2010). CaV1.2 and CaV1.3 are mainly localised post-synoptically to dendrites in neurons, particularly in soma, shafts and spines (Zamponi et al., 2015). The $Ca+^{2}$ currents conducted by these channels regulate neuronal excitability, shape neuronal firing or activate Ca^{2+} signalling pathways controlling

gene expression, which is referred to as the excitation-transcription coupling (ETC). In brief, perhaps what we can conclude from the literature is that the importance of Cav1.2 and Cav1.3 in modulating depressive-like symptoms lies in their potential regulation of the neurogenesis process and synaptic plasticity. These neurobiological functions are essential for a broad range of psychiatric diseases, making them a possible therapeutic target for depression, bipolar depression (BD), schizophrenia, attention deficit hyperactivity disorder and autism disorders. $Ca_V1.2$ and $Ca_V1.3$ are involved in the regulation of gene transcriptional events controlling neurogenesis and synaptic plasticity, each with a distinct function based on their brain location (Kabir et al., 2017, Lee et al., 2016, Marschallinger et al., 2015, Kim et al., 2017a, Nanou and Catterall, 2018).

The precise mechanism by which $Ca_V1.2$ and $Ca_V1.3$ influence the neurogenesis process remains unknown. One potential mechanism is via regulating gene transcription, hence, the release of the brain-derived neurotrophic factor (BDNF) from the hippocampal neurons. BDNF is a member of the neurotrophin family polypeptides, which is vital to the regulation of neural processes in neurogenesis, such as proliferation, differentiation and modification of synaptic plasticity, including the establishment of hippocampal long-term potentiation (LTP) (Martinowich et al., 2007). Ca^{2+} influx through L-VGCC serves as a primary source for the transcriptional up-regulation of BDNF through the activation of cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB) and major Ca^{2+} response elements (Aimone et al., 2014, Kabir et al., 2017). BDNF enhances synaptic plasticity and neurogenesis through activating Tropomyosin-Related Kinase B Receptors (TrkB) signalling.

1.2.6.3 **Genetic variation in L-VGCC and depression**

Studies attempting to link depression with genetic variations in CACNA1C and CACNA1D genes (coding $Ca_V1.2$ and $Ca_V1.3$, respectively) provide additional evidence. Rao et al. (2016) conducted a systematic review and meta-analysis to explore the association between CACNA1C variants and depression. Pooling the results from six studies, including one GWAS, showed that CACNA1C is strongly associated with depression. The authors also identified potential single nucleotide polymorphisms (SNPs) thought to increase the risk of depression. Among these SNPs, 1006377 within the CACNA1C emerged as one of the most highly replicated

SNPs, significantly associated not only with depression but also with broad neuropsychiatric disease (Rao et al., 2016). This SNP has also been found to affect the clinical response to antidepressant treatment in a biphasic manner (Fabbri et al., 2019). Similar to CACNA1C, genetic variants in CACNA1D (non-coding SNP rs893363) were found in GWAS to be associated with depression and other neuropsychiatric diseases(Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013).

1.2.6.4 **CCBs**

Based on the chemical structure, CCBs were divided into three subclasses: phenylalkylamines (e.g. verapamil), benzothiazepines (e.g. diltiazem) and dihydropyridines (e.g. nifedipine, amlodipine and isradipine). The phenylalkylamine and benzothiazepine CCBs are also known as non-dihydropyridine CCBs. All CCBs induce a vasodilatation effect to reduce BP as their primary mechanism of action. The vasodilator potency of CCBs varied considerably according to the subclass, with dihydropyridine-type compounds being comparably more potent than the phenylalkylamine and benzothiazepines groupings(Sica, 2006). The main cardiovascular indications for CCB include hypertension, coronary spasm, angina pectoris, supraventricular dysrhythmias, hypertrophic cardiomyopathy and pulmonary hypertension. CCB have also been used in other conditions involving peripheral vasospasm (i.e. Raynaud's phenomenon).

Mechanism of action: CCBs primarily act by inhibiting the influx of Ca^{+2} through the L-VGCC, resulting in lowering the peripheral resistance and subsequently enhancing vascular smooth muscle relaxation and reducing myocardial contractility.

Regarding tissue selectivity, unlike dihydropyridine, diltiazem and verapamil are more selective to cardiac muscle than vascular smooth muscle, reducing cardiac contractility and heart rate. CCB is generally considered selective to cardiac and vascular smooth muscle because L-VGCC in other tissues, such as skeletal, bronchial and tracheal muscle, are relatively insensitive to CCB. Studies have shown that dihydropyridine has a minimal effect on neuronal tissue, suggesting that these tissues are also less sensitive to CCB and are therefore associated with low central nervous system (CNS) side effects (Ferrari, 1997). However, findings

from human data demonstrated that dihydropyridine CCB can affect the LTP and L-term depression at the therapeutic dose, indicating that dihydropyridine CCB may also induce adverse CNS effects (Ortner and Striessnig, 2016). In general, the three subclasses of CCB have comparable pharmacokinetics properties (Sica, 2005). They have low and variable bioavailability, rapid onset of action, high protein binding (70%–98%) and high first pass metabolism. Most CCBs have a half-life between 1.3 and 6 hours, except for amlodipine, which has a half-life of 35-50 hours. Most CCBs are primarily excreted renally after metabolism.

1.2.6.5 **Role of CCBs in depression**

The putative association between CCB and depression has been contentious. In the late 1980s, several case reports and case series were published of substantial depression among patients treated with CCBs (Hullett et al., 1988, Biriell et al., 1989). These were followed by a cross-sectional ecological study conducted by Lindberg and colleagues with 152 Swedish patients. The authors revealed that CCB users faced a significantly higher risk of suicide (relative risk for suicide of 5.4, 95% CI 1.4–20.5) compared to non-users (Lindberg et al., 1998). Nonetheless, the study was extensively criticised in the literature because of the limited number of observations used to draw the conclusion. In another study, Hallas (1996) used a technique known as prescription sequence symmetry to analyse a large computerised prescription database. The author also analysed data from other antihypertensive classes, including CCBs and angiotensin converting enzyme inhibitors (ACEIs). The main findings of the study showed that CCBs and ACEIs, but not BBs, have a depression-provoking effect (Hallas, 1996). Rathmann et al. (1999) carried out a case-control study to identify an association between CCBs, BBs, ACEI and depression in diabetic patients. The study enrolled 972 diabetic cases who were newly diagnosed with MDD and matched with 972 diabetic controls for age, sex and index date. Eligible patients were newly exposed to antihypertensive medication for six months prior to the index date. Their findings showed that CCBs (OR = 2.2, 95% CI 1.2–4.2) and BBs (OR = 2.6, 95% CI 1.1–7.0) were strong predictors for depression occurrence. In an additional analysis, the authors assessed whether the association could be explained by the level of the daily prescribed dosage and they found that patients exposed to a high level of CCBs and BBs during the previous six months were at a four-fold higher risk of developing depression than those who did not (Rathmann et al., 1999). In a prospective cohort study, Ried et

al. (2000) followed 1,660 elderly patients for two years after a one-year exposure to antihypertensive treatment. and found a significant association between CCBs and depression On the other hand, several studies with different designs failed to detect any association between CCBs and depression (Agustini et al., 2020, Gerstman et al., 1996, Johnell and Fastbom, 2008, Patten and Lavorato, 2001).(Agustini et al., 2020)

Owing to the recent advanced knowledge about the biological role, the pharmacological effect and the genetic variation of L-VGCC in modulating some major psychiatric diseases, it was worth considering repurposing CCBs as a therapeutic agent in the psychiatric field. In general, the efficacy of CCBs was predominantly investigated in relation to BD. In the context of BD, the available evidence for CCB efficacy showed mixed results. To date, one comprehensive meta-analysis has examined the effects of CCBs on BD. However, the results of this study comprising six RCTs and 17 observational studies failed to provide evidence of any beneficial effect of CCBs on BD (Cipriani et al., 2016). Nonetheless, a more recent meta-analysis studying the cellular Ca^{+2} signalling in patients with BD showed that unmedicated BD patients had an excessive elevation of basial intracellular Ca^{+2} (Harrison et al., 2019), providing strong evidence for the plausible use of CCBs for this condition. Thus, until recently, CCBs have continued to be an experimental treatment for BD (Atkinson et al., 2019). CCBs have also been studied in depression treatment as a monotherapy or as adjunct therapy, but the results were largely inconsistent. An early trial found that in depressed patients receiving electroconvulsive therapy, there was greater mood improvement among those taking nicardipine compared with a placebo (Huffman and Stern, 2007). Tully et al. (2018) supported this finding after conducting a prospective cohort study of 269 depressed patients treated with SSRI and anti-hypertensive medication. The findings revealed that patients taking SSRIs and CCBs showed greater improvements in their depression scores compared to patients taking SSRIs and other antihypertensives; however, the effect was not statistically significant at 10-year follow-ups. Resent study also support this finding suggesting that CCBs may reduce the risk of developing depression (Kessing et al., 2020). Nonetheless, the results from other observational studies were discouraging, showing that CCBs could increase the risk of depression (Boal et al., 2016, Cao et al., 2019, Shaw et al., 2019).

To date, the risk of depression related to CCBs is inconclusive, and study findings fail to consistently support a single view of their association; thus, further studies are needed to establish the exact relationship.

Table 1-3 Description of VGCC types, function and pharmacology

Ca2+ current type	Channel	α1-subunit	Gene name	Channel distributions	Principle physiological function	Specific blocker	Associated psychiatric disorders	Pharmacological significance
L	CaV1.1	α_{1S}	CACNA1S	Skeletal muscle transverse tubules	Excitation-contraction coupling	Dihydropyridines; phenylalkylamines; benzothiazepines		Not established
	CaV1.2	α_{1C}	CACNA1C	Cardiac myocytes; smooth muscle myocytes; endocrine cells; neuronal cell bodies; proximal dendrites	Excitation-contraction coupling; hormone release; regulation of transcription; synaptic integration	Dihydropyridines; phenylalkylamines; benzothiazepines	ASD,SCZ,BD,MDD,ADHD	Mediates cardiovascular effects of clinically used Ca^{+2} antagonists; high concentrations of dihydropyridines exert antidepressant effects through Cav1.2 inhibition
	CaV1.3	α_{1D}	CACNA1D	Endocrine cells; neuronal cell bodies and dendrites; cardiac atrial myocytes and pacemaker cells; cochlear hair cells	Hormone release; regulation of transcription; synaptic regulation; cardiac pacemaking; hearing; neurotransmitter release from sensory cells	Dihydropyridines; phenylalkylamines; benzothiazepines	ASD,SCZ,BD,MDD,ADHD	Hypothetical drug targets for modulators of heart rate, antidepressant drugs and drugs for hearing disorders
	CaV1.4	α_{1F}	CACNA1F	Retinal rod and bipolar cells; spinal cord; adrenal gland; mast cells	Neurotransmitter release from photoreceptors	Dihydropyridines; phenylalkylamines; benzothiazepines		Not established
P/Q	Cav2.1	α_{1A}	CACNA1A	Nerve terminals and dendrites; neuroendocrine cells	Neurotransmitter release; dendritic Ca^{+2} transients; hormone release	ω-agatoxin	SCZ,ADHD, MDD	Inhibit neurotransmission in the mammalian CNS
N	Cav2.2	α_{1B}	CACNA1B	Nerve terminals and dendrites; neuroendocrine cells	Neurotransmitter release; dendritic Ca^{+2} transients; hormone release	ω-conotoxin	SCZ,ASD,MDD	Intratehecal administration of SNX-111 reduce pain in patients unresponsive to intrathecal opiates

Ca2+ current type	Channel	α1-subunit	Gene name	Channel distributions	Principle physiological function	Specific blocker	Associated psychiatric disorders	Pharmacological significance
R	Cav2.3	α_{1E}	CACNA1E	Neuronal cell bodies and dendrites	Repetitive firing; dendritic calcium transients	SNX-482	SCZ,ASD,MDD	The tarantula toxin SNX-482 blocks exogenously expressed Cav2.3 currents but is only partially effective on native cerebellar R-type currents
T	Cav3.1	α_{1G}	CACNA1G	Neuronal cell bodies and dendrites; cardiac and smooth muscle myocytes	Pacemaking; repetitive firing	None	ASD	May mediate effect of absence antiepileptic drugs such as ethosuximide and other thalamocortical dysrhythmias
	Cav3.2	α_{1H}	CACNA1H	Neuronal cell bodies and dendrites; cardiac and smooth muscle myocytes	Pacemaking; repetitive firing	None	ASD,SCZ	May mediate effect of absence antiepileptic drugs such as ethosuximide and other thalamocortical dysrhythmias; potential drug target in hypertension and angina pectoris
	Cav3.3	α_{1I}	CACNA1I	Neuronal cell bodies and dendrites; cardiac and smooth muscle myocytes	Pacemaking; repetitive firing	None	ASD,SCZ,ADHD	May mediate effect of absence antiepileptic drugs such as ethosuximide and other thalamocortical dysrhythmias

Adapted and modified from Andrade et al. (2019), Catterall et al. (2005). Abbreviations: ADHD, attention-deficit and hyperactivity disorder; ASD, autism spectrum disorder, BD, bipolar disorders; Ca^{2+}, calcium, CNS, central nervous system; DHPs, dihydropyridines; MDD, major depressive symptoms; SCZ, schizophrenia;

1.2.7 BBs and risk of depression

1.2.7.1 β-adrenergic receptors (βARs)

βARs are essential components of the SNS mediating the effect of endogenous catecholamines, including adrenaline (A) and noradrenaline (NA). There are distinct subtypes of βARs; each has a unique pharmacological function based on their tissue localisation. $ß_1$AR is. predominantly located in the heart and kidney facilitating myocyte contraction and renin release, whereas $ß_2$AR is more predominant in the lung and blood vessels mediating smooth muscle relaxation. $ß_1$AR and $ß_2$AR are also located in the liver. $ß_3$AR is predominant in adipose tissue and exclusively in brown adipose tissue present in rodents and new-born humans. βARs have also been detected in several brain areas, such as the hippocampus, cerebellum, thalamic nuclei, basal ganglia, midbrain and cerebral cortex (Reznikoff et al., 1986). $ß_1$AR and $ß_2$AR may coexist in the same tissue and facilitate the same physiological functions. For example, in the hippocampus, $ß_1$AR and $ß_2$AR were found to regulate synaptic plasticity. All βARs belong to the G-protein coupled receptor (GPCR) family, which utilises a variety of second messengers in response to a binding ligand to provoke a cellular function. βARs can signal via stimulatory G-protein activating adenylyl cyclase (AC), which mediates the conversion of adenosine triphosphate (ATP) into cAMP (Frishman, 2007). Elevating the levels of cAMP triggers further downstream signal transduction, resulting in a functional response.

1.2.7.2 Role of βARs in depression

The locus coeruleus (LC) is a cluster of NA-containing neurons that are located in the dorsal pontine tegmentum. Hyperactivation of these neurons is thought to be associated with depression induced by stress (Sara, 2009). Under stress conditions, acute activation of the LC results in the secretion of NA and subsequently stimulates the adrenergic receptors in the PVN in the hypothalamus, which in turn aggravates stress by activating the HPA axis (Seki et al., 2018). Therefore, the noradrenergic innervation from the LC to the hypothalamus is important for activating the critical step (i.e. the HPA axis) related to stress. However, long-term stress can cause a prolonged activation of the HPA axis and eventually lead to neurodegeneration or retraction of the noradrenergic neurons in the LC. In

response to these neurological alterations (i.e. impairment of the LC), changes in βARs in terms of the functionality and number of receptors may occur (Brunello et al., 2003). Recent studies have illustrated that βARs play a critical role in regulating potential brain functions, such as cognition and memory, and they contribute to the pathogenesis of Alzheimer's Disease, Parkinson's disease and depression (Gannon et al., 2015, Hagena et al., 2016, Seki et al., 2018). The stimulation of βARs following the activation of noradrenergic neurons may enhance hippocampal synaptic plasticity and hippocampal neurogenesis, which are thought to be important therapeutic components of antidepressants. Several studies have confirmed the role of β_1AR and β_2AR in promoting synaptic plasticity (Hagena et al., 2016). Antidepressants and rapid acting antidepressants have shown some efficacy in reversing stress-induced neural remodelling and hippocampal shrinking through the upregulation of BDNF(Lee and Kim, 2008, Sun et al., 2016a) This antidepressant effect is thought to be mediated through βAR activation, which stimulates cAMP/PKA/CREB/BDNF downstream signalling (Seki et al., 2018, Hagena et al., 2016). The proposed mechanism of action might be restricted to antidepressants that increase synaptic NA levels by blocking the action of NA transporters at the presynaptic side and sustain synaptic plasticity, particularly LTP, which is considered an important beneficial effect of antidepressants (Seki et al., 2018) (**Figure 1-3**). Qian et al. (2017) proposed that stimulated β_2AR can interact with both the Cav1.2 channel and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) postsynaptically, forming two distinct complexes supporting the generation process of the LTP in response to brain wave frequency (**Figure** 1-4**)**. Genetic studies provide another line of evidence that emphasises the role of βAR in depression. The ADRB1 gene coding the β_1AR has been the most investigated candidate gene. ADRB1, mediating the effect of A and NA, has been linked to the regulation of mood, memory, autonomic function, neuro endocrine activity, BP, and response to anti-depressants treatment (Amare et al., 2017, Fabbri et al., 2013).

1.2.7.3 **BB**

BBs were one of the first-line therapies for primary hypertension dating back to 1977, as recommended by the first report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (JNC 1) (Ripley and Saseen, 2014). However, following RCTs and meta-analyses, the current

recommendation suggests using BBs as an add-on therapy with other antihypertensive medications (Hackam et al., 2013). BBs are now mainly indicated for patients suffering from CHD, especially after an MI event, stroke or HF. BBs can be classified according to their pharmacological properties into three generations of agents. Propranolol is the prototype of the first generation, which exerts equal blockades of β_1AR and β_2AR and is thus characterised as a non-selective BB. The second generation is termed a selective BB, as it possesses a higher affinity towards β_1AR than β_2AR, though the extent of the selectivity varies among the agents of this generation, which includes metoprolol, bisoprolol and atenolol. In most cases, non-selective BBs are effective as selective BBs; however, selective BB agents have the advantage of fewer side effects associated with blocking β_1AR, such as bronchospasm. The third generation includes labetalol, carvedilol and bucindolol, which are distinguished from the two previous generations by their ability to block α_1-adrenergic receptors inducing vasodilatation. Furthermore, some BBs, such as pindolol, exhibit intrinsic sympathomimetic activity (ISA), meaning they can act as an agonist mimicking the transmission of SNS signalling; however, the clinical significance of this effect is uncertain.

Table 1-4 displays some pharmacodynamic and pharmacokinetic properties possessed by an individual BB, which include bioavailability, lipophilicity, ISA, elimination half-life and route of elimination. In terms of lipophilicity, BB can be divided into lipophilic and hydrophilic agents. Hydrophilic agents, such as atenolol and nadolol, are advantageous over hippophilic agents, such as propranolol, since they have lower CNS side effects (e.g. depression, psychosis and sleep disturbances). The mechanism by which BBs reduce BP is not fully understood. However, it is thought that BBs mainly act by inhibiting β_1AR located in the heart and reducing cardiac output, though a reduction in peripheral resistance may occur with long-term use. As the third generation of BBs can antagonise α1AR, this class can also reduce the peripheral resistance, thus mediating vasodilatation. By blocking the β_1AR in the juxtaglomerular apparatus, BBs decrease the release of renin by the kidney, resulting in decreased circulating angiotensin II (Ang II) and aldosterone and subsequently enhancing sodium and water excretion and further reducing peripheral resistance.

1.2.7.4 **BB and risk of depression**

After the introduction of propranolol for clinical uses in 1967, several studies reported its association with the onset of clinical depression. An early frequently cited study conducted by Waal (1967) reported that 50% of patients treated with propranolol hydrochloride (12mg/day) for more than three months developed depression. This kind of association was replicated by later case reports and RCT studies (Steiner et al., 1990). An increase in antidepressant usage among BB users was also observed (Avorn et al., 1986). It was hypothesised that BB decreases the noradrenergic activity in the brain(Patten and Love, 1993). Thus, highly lipophilic BBs, such as propranolol, that are more likely to cross the blood brain barrier (BBB) were considered more likely to cause depression. Thiessen et al. (1990) conducted the first longitudinal study in this regard to investigate the relation between BBs and the incidence of antidepressant prescription. They recruited 3,218 patients who were free of a BB prescription for six months prior to the study. Over a 12-month follow-up period, they found that propranolol in particular, but not other lipophiliic or hyprophilic BBs, was associated with an increased risk of antidepressant prescription, proposing that the depressogenic activity is a unique feature restricted to propranolol that is irrelevant to its lipophilicity property (Thiessen et al., 1990). However, this finding was refuted by Sørensen and colleagues, who examined the association between different classes of antihypertensive medications and risk of suicide, which was considered in this study as a specific indicator for severe depression. In a six-year follow-up, they found a significant increase in suicide risk among new BB users (standardised mortality ratio = 1.6 95% CI 1.2, 2.1) compared to non-BB users, especially during the first year of treatment. After stratification by the degree of lipid solubility, the risk of suicide was confined to BBs with medium and high lipid solubility, and no significant association was observed with low lipid solubility, suggesting a dose-response association (Sørensen et al., 2001). This was contradicted by other studies suggesting a null association between BB and depression (Crane et al., 2006, Patten and Lavorato, 2001). Dhondt et al. (2002) showed that BBs are significantly associated with an increased risk of depression; however, after performing an additional analysis, the significant positive association remained only for non-selective BBs (OR = 1.08, 95% CI 1.08–3.10) and not for selective BBs (OR = 1.39 95% CI 0.99–1.96). Ried et al. (2000) proposed that positive or negative

findings regarding the association between BBs and depression is a matter of how depression is measured.

Two meta-analyses summarised studies investigating the association between BBs and depression, but they provided inconsistent evidence. The findings from the first meta-analysis of 11 RCTs suggested an increased risk of depression in users of propranolol (Patten, 1990). However, the results obtained a decade later by Ko et al. (2002), who pooled the results from seven RCTs with a maximum follow-up duration of four years and a total number of 100,662 patients, showed that neither BBs (RR = 1.12, 95% CI 0.89, 1.41) nor high lipid soluble BBs were significantly associated with depressive symptoms. Contradictory results have been continued to publish on this subject in recent years showing either positive or negative effect of BBs on depression. Researches with different study designs including cross-sectional (Agustini et al., 2020), case-control (Cao et al., 2019) and prospective studies (Boal et al., 2016, Shaw et al., 2019) reported a positive association between BBs and risk of depression. Nonetheless, in a large case-control study with more than 3 million subjects, Kessing et al. (2020) have strongly challenged these results, suggesting that BB as a class is associated with a reduced risk of depression. Certain BBs have been suggested to augment the treatment of depression. Pindolol, in particular, has been found to accelerate antidepressant responses during therapy for refractory depression (Sokolski et al., 2004). This finding is mainly due to its structural homology to serotonin that underlies its capacity to act as an antidepressant-augmenting agent at the level of the serotonin receptor (Barowsky and Schwartz, 2006). Several studies have evaluated pindolol as an augmentation agent of antidepressants in treatment-resistant depression; however, data from the largest studies failed to detect any significant effects (Anderson et al., 2008).

As shown, these studies spanning five decades report conflicting results and the long-standing concern about whether BBs increase the depression risk has not been resolved, thus meriting further investigation.

Table 1-4 Pharmacodynamic/pharmacokinetic properties of BB

Generation	BB	Bioavailability	Lipid solubility	ISA	E $t_{1/2}$ (h)	Route of elimination
1st generation (non-selective)	Propranolol	49-60%	High	-	3-4	Hepatic
	Penbutolol	>90%	High	-	1-3	Hepatic
	Nadolol	20-30%	Low	-	14-24	Hepatic ± renal
	Oxprenolol	24-60%	High	-	1-3	Hepatic ± renal
	Timolol	50-75%	Low	-	5.5	Hepatic ± renal
	Sotalol	75-90%	Low	-	15	Renal ± hepatic
	Pindolol	90%	Low	+	3-4	Renal+ Hepatic
2nd generation (Selective)	Atenolol	50%	Low	+	6-9	Hepatic + renal
	Metoprolol	50%	Moderate	+	3-4	Hepatic
	Bisoprolol	88%	Low	+	10-12	Renal + Hepatic
	Acebutolol	40-60	Low	+	7-13	Hepatic ± renal
3rd generation B – with alpha	Carvedilol	25	Moderate	-	7	Hepatic
	Nebivolol	12	Low	+	22	Hepatic
	Betaxolol	80	Low	+	14-20	Hepatic ± renal
	Carteolol	90	Low	-	7	Renal+- Hepatic

Abbreviations: ±, elimination is less than 30%; BB, Beta blocker; E $t_{1/2}$, elimination half-life; h, hour; ISA, Intrinsic sympathetic activity
Data adapted from (Borchard, 1998)

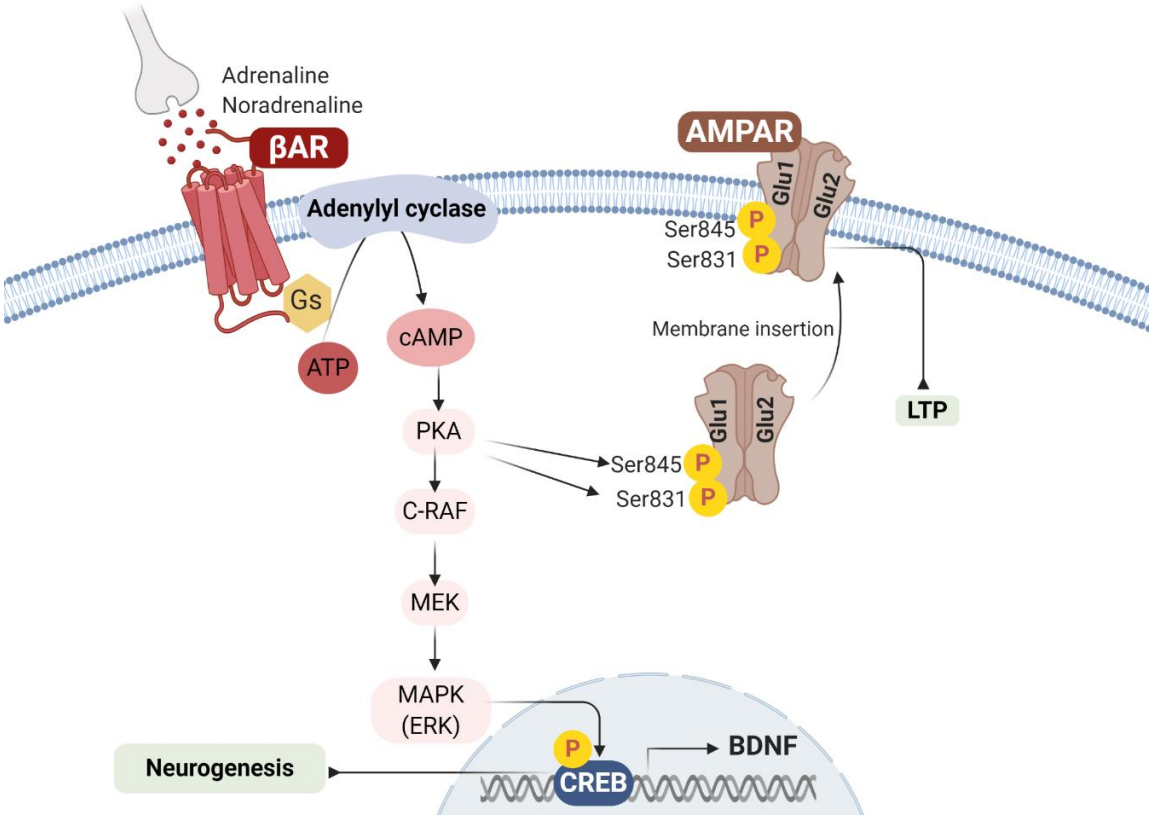

Figure 1-3 Role of βAR inducing hippocampal synaptic plasticity and neurogenesis mediating antidepressants effect

Figure modified from [(Hagena et al., 2016, Seki et al., 2018). Stimulation of βAR coupled to Gs protein by adrenaline or noradrenaline results in activation of adenylyl cyclase and formation of cAMP. cAMP activates PKA and subsequently ERK/MAPK which eventually activates the CERB which in turn enhances the expression of the BDNF and other proteins promoting neurogenesis. In a second pathway, PKA phosphorylates the GluA1 subunit of the AMPAR at Ser845 and Ser 831 facilitating membrane insertion of the Glu1 and consequently maintains LTP. Abbreviations: AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; ATP, adenosine triphosphate; βAR, beta adrenergic receptors; BDNF, brain derived neurotrophic factor; cAMP, cyclic adenosine monophosphate, C-Raf, RAF proto-oncogene serine/threonine kinase; CREB, cAMP-responsive element-binding protein; ERK, extracellular signal-regulated kinase; Glu1, glutamate receptor subunit 1; Glu2, glutamate receptor subunit 2; Gs, stimulatory G protein; LTP, long-term potentiation; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase; PKA, protein kinase A.

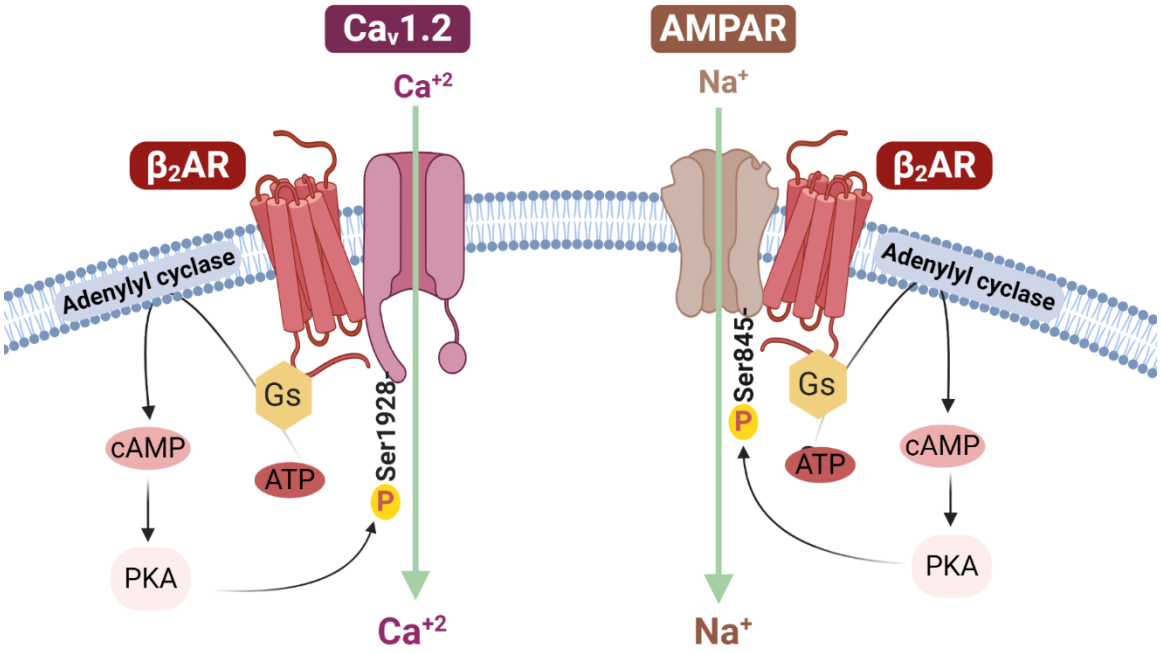

Figure 1-4 Role of βAR mediating postsynaptic calcium channel signalling in LTP
Figure reproduced with permission from (Qian et al., 2017). Stimulation of βAR that are specifically bound to AMPAR and $Ca_v1.2$ results in activation of these receptors through phosphorylation of Ser1928 on $Ca_v1.2$ and Ser845 on AMPA by the PKA. The phosphorylated AMPAR cause Na^+ influx and depolarisation during synaptic transmission in response to theta stimulation., while the phosphorylated $Ca_v1.2$ enhances Ca^{+2} entry and therapy cause an increase in synaptic strength LTP. Abbreviations: AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; ATP, adenosine triphosphate; β_2AR, beta adrenergic receptors type 2; cAMP, cyclic adenosine monophosphate; $Ca_v1.2$; calcium channel receptor; Gs, stimulatory G protein; LTP, long-term potentiation; PKA, protein kinase A.

1.2.8 The RAS antagonists and risk of depression

1.2.8.1 The RAS

It is now well accepted that all components of the RAS are present within the brain. The central and peripheral pathways of RAS in the brain play a potential role in regulating different functions and patterns, including cerebral circulation, cerebroprotection and other neuropsychiatric diseases, such as depression (Jackson et al., 2018b, Labandeira-Garcia et al., 2014, Vian et al., 2017, Wright and Harding, 2011). The main peripheral pathway of RAS is the forebrain pathway comprising the circumventricular organs (CVOs) that are connected to the peripheral RAS via fenestrated capillaries. Brain structures surrounding the forebrain pathway have access to the peripheral RAS component. However, the BBB restricts the peripheral RAS from accessing the majority of the brain regions, making local synthesis of the cerebral RAS components essential. The central pathway integrates the hypothalamus and medulla, being the primary source of local angiotensin synthesis.

The RAS can exert its main biological functions through the traditional pathway, also named classic RAS and through the non-classic pathway (Romero et al., 2015). **Figure** 1-5 **(a),** schematically presents the components of the RAS illustrating its common pathways. The classical pathway of RAS begins with the synthesis of renin from the pro-renin, which then cleaves angiotensinogen to angiotensin I (Ang I) and subsequently Ang I is converted by Ang converting enzyme (ACE) into Ang II, which is the most powerful biologically active product of RAS (Unger, 2002). Studies of the adult human brain revealed that Ang II actions in the CNS are mediated by the activation of angiotensin 1 (AT1) and angiotensin 2 (AT2) receptors. The classic effects of Ang II are predominantly mediated by the AT1 receptor, which is a GPCR that initiates signal transduction and regulates gene transcription (Wright and Harding, 2011). In the brain, the AT1 receptor is particularly dense in the HPA axis, the anterior pituitary, the CVOs, the PVN, the preoptic and the supraoptic nuclei of the hypothalamus (Wright and Harding, 2011).

In the circulation, activation of AT1 receptor results in vasoconstriction, reabsorption of sodium and water, and production of aldosterone (Romero et al.,

2015). Stimulation of the AT1 receptor is also implicated in multiple pathways, including stress response and the release of inflammatory biomarkers (Benicky et al., 2011). Recently, a non-classical RAS pathway was discovered and is considered a counterregulatory pathway of the classical RAS actions formed by ACE, Ang II and the AT1 receptor (Santos et al., 2013). The identification of ACE 2, a homology to ACE, unravels the existence of a distinct enzymatic pathway for the degradation of Ang I and Ang II (Patel et al., 2016). This enzyme can convert Ang II into angiotensin 1-7 (Ang 1-7). It can also transform Ang I into angiotensin 1-9 (Ang 1-9), which is then converted to Ang 1-7 by ACE (Patel et al., 2016). Ang 1-7 binds to the MAS1 receptor, a G-protein-coupled receptor, and elicits a vasodilation of blood vessels by an endothelium-dependent release of nitric oxide (Brosnihan et al., 1998).

1.2.8.2 **The classical RAS antagonist**

The classical inhibitors of the RAS can be classified into four groups: renin inhibitor , ACEIs, angiotensin receptor blockers (ARBs), and mineralocorticoid receptor blockers (**Figure** 1-5 **[a])**. The following section focuses on the two main types of RAS, including ACEIs and ARBs, considering their mechanisms of action, pharmacokinetics, and pharmacological and clinical effects.

ACEIs: In the early 1980s, captopril was proposed as the first oral ACEI after proving its effectiveness in controlling BP and improving clinical outcomes of patients with HF (Dzau et al., 1980). Since then, ACEI has been proven as a treatment for a wide range of CVD and kidney-related conditions, including hypertension, HF, left ventricular dysfunction, MI and diabetic nephropathy (Brown and Vaughan, 1998). ACEIs have been classified according to the chemical structure of their active moiety into three groups: sulfhydryl, carboxyl and phosphinyl. Captopril is the prototype of the sulfhydryl-containing ACEIs; the other members of this group are fentiapril, pivalopril, zofenopril and alacepril. The carboxyl-containing group represents the majority of ACEIs, which include enalapril, benazepril, lisinopril, ramipril, quinapril, perindopril and trandolapril. Fosinopril is the only phosphinyl-containing ACEI that has been approved by the Food and Drug Administration (FDA) (Brown and Vaughan, 1998). The main differences between the three groups are not limited to the chemical structure, as they also have different potency, bioavailability, elimination pathways, half-

lives, distribution and binding affinity. **Table 1-5** summarises the pharmacokinetics properties of ACEIs. Of all the ACEIs, fosinopril has the greatest lipophilicity, meaning it can cross the BBB, while lisinopril has the least. Other ACEIs that are able to cross the BBB are ramipril, captopril, quinapril and trandolapril. The potency of ACEIs measures the amount of ACEIs required to inhibit 50% of ACE plasma activity. The relative potency and ability to bind tissue ACE of ACEIs is quinaprilat = benazeprilat > ramiprilat > perindoprilat > lisinopril > enalapril > fosinopril > captopril (Lala and McLaughlin, 2008). Regarding the route of elimination, the majority of ACEIs are cleared by the kidney except for fosinopril, trandolapril and spirapril. The most common adverse effects are a cough (6%–20% of patients) and angioedema (1% of patients) (Romero et al., 2015, Sánchez-Borges and González-Aveledo, 2010).

ACEIs act mainly by blocking ACE, preventing the conversion of Ang I to Ang II and resulting in the vasodilatation of blood vessels. Blocking ACE may also shift the balance of RAS towards the ACE2–Ang (1-7) MAS1 axis (Figure 1-5 [a]) and suppress the degradation of Ang (1-7) to an inactive metabolite. This causes an increase in the plasma level of Ang (1-7)–MAS1, thus producing a cardioprotective effect (Miller and Arnold, 2019).

Table 1-5 Summary of pharmacokinetic properties of ACEI

Chemical group-containing ACEI	ACEI	Active metabolite	Protein binding (%)	Bioavailability	E $t_{1/2}$ (h)	Execration
Suphyhydryl-containing	Captopril	None	30	75-91	2	Renal
Carboxyl-containing	Benazepril	Benazeprilat	90-97	37	10-11	Renal ± Hepatic
	Enalapril	Enalaprilat	13-50	60	11	Renal
	Lisinopril	None	3-10	6-60	12	Renal
	Moexipril	Moexiprilat	50	13	2-9	Renal + Hepatic
	Perindopril	Perindoprilat	10-20	74	3-10	Renal
	Quinapril	Quinapril diacid	97	>60	2	Renal
	Ramipril	Ramiprilat	56	50-60	9-18	Renal + Hepatic
	Trandolapril	Trandolaprilat	80-94	70	15-24	Renal + Hepatic
Phosphoril-containing	Fosinopril	Fosinopril acid	89-100	36	12	Renal + Hepatic

Abbreviations: ±, less than 30% hepatic elimination when renal function normal; ACE, angiotensin-converting enzyme inhibitors; E $t_{1/2}$, elimination half-life; h, hour.
Data adapted from (Brown and Vaughan, 1998, Thomas and Tomlinson, 2008)

ARBs: Losartan is the first oral ARB that has been approved for clinical use since 1995 (Ripley and Hirsch, 2010). At present, nine orally active ARBs are available on the market: losartan, candesartan, irbesartan, olmesartan, telmisartan, valsartan, eprosartan, fimasartan and azilsartan. Generally, the clinical indication for ARBs is the same as that for ACEIs, and both have shown comparable efficacy (Messerli et al., 2018). In terms of tolerability, ARBs are better tolerated than ACEIs as they are associated with fewer side effects than ACEIs (Toh et al., 2012). Theoretically, as both ACEIs and ARBs supress the RAS activity, it is anticipated that a combination therapy would produce a pronounced beneficial cardiac effect. Nonetheless, studies have shown that a combination therapy achieves no additional benefit over single agent approaches and it could even lead to a harmful effect (Abraham et al., 2015, Phillips et al., 2007).

Most ARBs have long plasma elimination half-lives. Candesartan cilexetil and losartan potassium are prodrugs requiring further metabolism to elicit their therapeutic effect, while most ARBs are inherently active (Vallerand et al., 2019). The absolute bioavailability of ARBs is quite varied, ranging from a low of 13% for eprosartan to a high of 80% for irbesartan (Israili, 2000). Most ARBs are highly bound to plasma protein (>90%), but they differ substantially in their volume of distribution. ARBs are predominantly cleared from the circulation by the biliary system, while only a small proportion are eliminated through the kidney (Sica, 2001).

ARBs were specifically designed to inhibit Ang II from binding to the AT1 receptor, thus preventing the negative consequences after AT1 receptor activation. Similar to ACEIs, ARBs can increase the plasma level of Ang (1-7) by producing a reflexive increase in the production of ineffective Ang II, thus shunting the Ang II metabolism towards Ang (1-7) formation (Miller and Arnold, 2019). There is evidence that not all ARBs share the same pharmacological effects; some ARBs possess a unique molecular effect independent of AT1 receptor inhibition (Kurtz and Pravenec, 2008, Miura and Saku, 2010). For example, Wang et al. (2013) assessed six ARBs ability to slow the progression of Alzheimer diseases by reducing the accumulation of ß-amyloid protein in primary cortico-hippocampal neuron cultures derived from the Alzheimer mouse model expressing human amyloid precursor protein. The authors demonstrated that, only valsartan and to a lesser

extent losartan can cause a significant reduction of ß-amyloid levels with no evident cell toxicity (Wang et al., 2013).

1.2.8.3 **Role of the RAS in depression**

As described previously (See section 1.2.8.1), there are several subtypes of Ang and Ang receptors; however, it appears that the neurotoxic effect, particularly in depression, is predominantly ruled by the Ang II/AT1 receptor cascade. This section thus focuses mainly on this pathway, presenting evidence that investigates the functional relevance of the Ang II/AT1 receptor in depression. Ang II is considered a stress hormone based on several observations showing that Ang II can stimulate the stress response systems (i.e. HPA axis and SNS) through activating AT1 receptors centrally and peripherally (Saavedra and Benicky, 2007, Yang et al., 1993, Yang et al., 1996). Multiple pathways have been identified in the brain linking Ang II to stress; however, the Subfornical organ (SFO)–PVN connection is the best studied pathway (Bains and Ferguson, 1995, Ferguson, 2009). Studies on animal models have demonstrated that different types of stress can increase the formation of brain Ang II and the expression and transcription of AT1 receptors, particularly in the hypothalamic PVN and SFO areas (Saavedra and Benicky, 2007). In the PVN, AT1 receptors are highly expressed in the parvocellular corticotrophin-releasing neurons controlling the release of the corticotropin-releasing hormone (CRH). In response to stress, the HPA axis is activated and then stimulates the release of ACTH from the anterior pituitary gland, which in turn activates the immune system and signalling of other hormones, such as catecholamines and vasoactive peptides. The regulation of ACTH synthesis and secretion is governed by a number of neurotransmitters and peptides, such as Ang II. (Spinedi and Negro-Vilar, 1983). Ang II can stimulate ACTH secretion, either directly by acting on the pituitary corticotrophs (Aguilera et al., 1995) and/or indirectly by activating AT1 receptors in the PVN and subsequently enhancing the expression and secretion of the CRH and adrenal glucocorticoids, which eventually initiate the stress response cascade (**Figure** 1-5 **[b]**).

Furthermore, there is evidence that even circulating Ang II can act centrally after altering BBB permeability to produce Ang II as a neurotransmitters, resulting in initiating the stress response (Calvillo et al., 2019). Additionally, since the AT1 receptors are localised in the synaptic ganglia and nerve terminals, evidence

suggests that Ang II also enhances central sympathetic activity, thus regulating the secretion of catecholamines from the adrenal medulla and sympathetic nerves that are characteristic of stress (Saavedra and Benicky, 2007, Saxena, 1992). Overall, evidence generated from these studies correlates well with one of the major neuroendocrine alterations characterising major depression, the HPA axis and SNS dysfunction.

There is strong evidence of the major involvement of the Ang II/AT1 receptor in the initiation and regulation of inflammatory cascades centrally and peripherally, which has been implicated in the pathological process of depression (Figure 1-5 [c]). Ang II activates the AT1 receptor mediating the inflammatory process through several mechanisms. In the circulation, Ang II can induce proinflammatory effects on leucocyte, endothelial cells and the vascular smooth muscle through stimulating inflammatory mediators such as the reduced nicotinamide adenine dinucleotide phosphate dehydrogenese (NADPH), tumour necrosis factor-a (TNF-a), IL-6 and nuclear factor-kB (NF-kB) (Figure 1-5 [c]) (Dandona et al., 2007) predisposing to inflammation (Zhang et al., 1999, Dandona et al., 2007). The peripheral inflammatory response has been shown to trigger the development of atherosclerosis (Verdecchia et al., 2008); thus, since Ang II contributes to increased inflammation, it can also be considered a mediator of atherosclerosis, which has been linked to depression (Tiemeier et al., 2004). Evidence shows that primary inflammation that has occurred peripherally can further sustain and/or strengthen the pathophysiological cascades causing neuroinflammation, which has been linked to depression (Troubat et al., 2020). Research also shows that brain Ang II can induce a proinflammatory effect through stimulating oxidative stress, apoptosis and neuroinflammation causing neurodegenerative disorders (Abiodun and Ola, 2020) and mood disorders (Bakunina et al., 2015). Furthermore, Ang II can act directly on the microglial cells, which are one of the potential brain cells that have been recently linked to depression (Singhal and Baune, 2017) and hypertesion pathology (Shen et al., 2015). In the brain, microglial cells are considered the resident macrophage inducing a neural immune response (Lenz and Nelson, 2018). They are a major source of Ang II production, which can directly act on AT1 receptors on microglial cells, activating a neuronal and inflammatory effect (Gong et al., 2019). Researchers have observed that stressful conditions activate the innate inflammatory response of the microglial cells, resulting in

chronic neuroinflammation and consequently causing depressive-like symptoms in animal models (Qin et al., 2007). More recently, Zhang et al. (2018) demonstrated that inhibiting microglial activation can be a possible target for treating depression. There is strong evidence that ACEIs and ARBs can act as anti-inflammatory agents, ameliorating brain and peripheral inflammation by blocking the Ang II/AT1 receptor cascade in animal models (Benicky et al., 2011, Benicky et al., 2009, Pang et al., 2012, Saavedra, 2012, Gong et al., 2019). This evidence shows that Ang II mediates peripheral and central inflammation, which correlates highly with the inflammatory hypothesis of depression.

Furthermore, genetic studies have linked several functional polymorphisms of RAS-related genes to depression and suicidal behaviour. For example, the AT1 receptor genotype (A1166C) CC, which results in greater responses to Ang II at lower concentrations, has been shown to be associated with an increased risk of depression (Saab et al., 2007). Additionally, there is evidence that the ACE polymorphisms associated with enhanced ACE serum activity are able to influence responses to antidepressants (Bahramali et al., 2016) and could even be a risk factor for suicide (Fudalej et al., 2009).

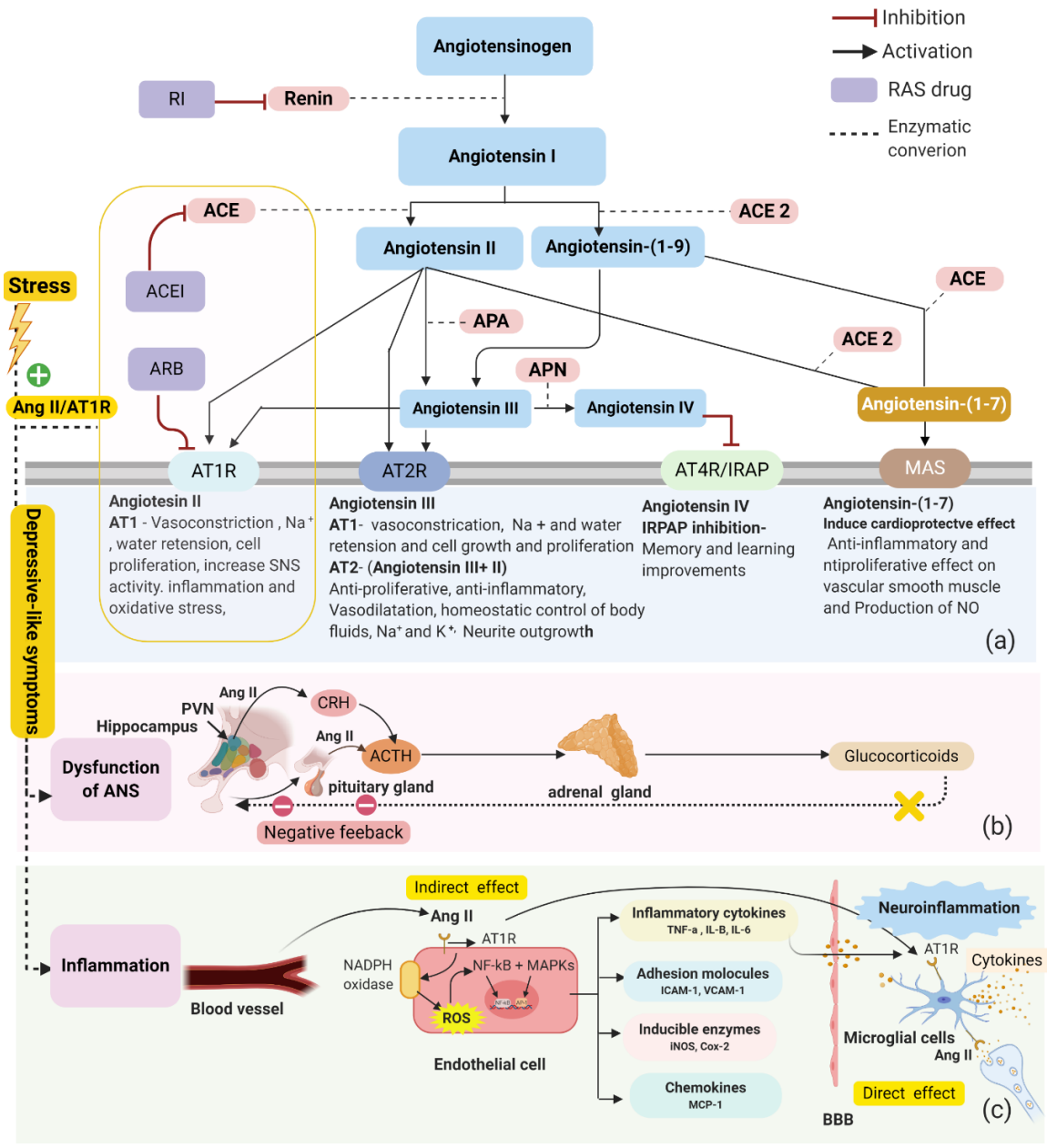

Figure 1-5 Components of RAS, main RAS cascades correlated with depressive-like symptoms, and RAS drugs interfering with Ang II/AT1 signaling.
Figure modified from [(Benicky et al., 2009, Guimond and Gallo-Payet, 2012, Riet et al., 2015, Romero et al., 2015, Saavedra and Benicky, 2007)]**. (a)** Renin cleaves angiotensinogen to angiotensin I which is the rate limiting step of the RAS and it can be blocked by RI. Angiotensin I is then converted to Angiotensin II by ACE which can be inhibited by ACEI. Angiotensin II acts directly on AT1R and AT2R receptors or undergoes further metabolism by APA producing Angiotensin III which further processed by APN to Angiotensin IV. Angiotensin IV inhibit the activity of IRAP receptor. Angiotensin II can be also metabolized by ACE2 producing angiotensin (1-7) activating MAS receptor. In a second pathway, Angiotensin I can be cleaved by ACE2 into angiotensin (1-9) and eventually to angiotensin (1-7) by ACE. **(b)** Stress is associated with autonomic dysfunction including hyperactivation of HPA-axis function; increased brain Angiotensin II formation and upregulation of AT1 receptors in the PVN in the hypothalamus. Angiotensin II enhance the activation of ACTH either indirectly through activating AT1R in the PVN mediating CRH secretion which in turn enhances ACTH production or directly through stimulating AT1R in the pituitary gland resulting in formation of ACTH. ACTH hormone stimulates adrenal gland to release glucocorticoids which regulates negative feedback inhibition of HPA-axis which is impaired under stress resulting in a sustain activation of HPA-axis function and depressive-like symptoms. **(c)** Ang II/AT1R also promotes inflammatory cascades centrally and peripherally; In the circulation, Angiotensin II activates AT1R in endothelial cell enhancing immune response signaling. Angiotensin II/AT1R stimulates the production of inflammatory mediators such as NADPH and ROS resulting in transcription of proinflammatory

factors including but not limiting to cytokines (TNF-a, IL-B, IL-6), Adhesion molecules (ICAM-1, VCAM-1), Inducible enzymes (iNOS, Cox-2) and chemokines (MCP-1). Pro-inflammatory cytokines and angiotensin II can penetrate BBB activating microglial cells inducing cell injury and neuroinflammation. Angiotensin II within brain can act directly on AT1R resulting in microglial activation and initiation of inflammatory signaling inducing depressive-like symptoms. **Abbreviations:** ACE, angiotensin converting enzyme; ACE2, angiotensin converting enzyme 2; ACEI, angiotensin converting enzyme inhibitor; Ang II, angiotensin II; ANS autonomic nervous system; APA, aminopeptidase A; APN, Aminopeptidase N; ARB, angiotensin receptor blockers; AT1R, type-1 angiotensin receptor angiotensin; AT2R, type-2 angiotensin receptor; AT4R/IPRA, type-4 angiotensin receptor/insulin-regulated membrane aminopeptidase or insulin-responsive aminopeptidase; BBB, blood brain barrier; COX-2, cyclooxygenase 2; HPA-axis, hypothalamus-pituitary adrenal axis; ICAM-1, intercellular adhesion molecule 1; IL-6, interleukin-6, IL-B, interleukin-B; iNOS, inducible nitric oxidase; MAPKs, mitogen activated protein kinases; MCP-1 - monocyte chemotactic protein-1; NADPH, nicotinamide adenine dinucleotide phosphate; NFκB, nuclear factor κB; PVN, paraventricular nucleus; RI, renin inhibitor; ROS, reactive oxygen species; TNF-a, tumor necrotic factor-a, VCAM-1 - vascular cell adhesion molecule 1.

1.2.8.4 **RAS antagonist and depression**

In the 1980s, several case reports from clinical studies revealed that depressed patients using ACEIs experienced a substantial mood elevation (Germain and Chouinard, 1988, Hertzman et al., 2005, Zubenko and Nixon, 1984). However, the study conducted by Patten et al. (1996) was the first epidemiological study reporting an association between ACEIs and depression risk. The authors conducted a case-control study to evaluate the associations between CCBs, BBs, digoxin, ACEI and clinical diagnoses of depressive disorders in hospitalised patients. They showed that hypertensive patients, particularly, female and elderly patients who had exposed to ACEI were more likely to exhibit depressive symptoms, an association that was not found with the other drugs (Patten et al., 1996). Meanwhile, Gerstman et al. (1996) refuted any evidential links between ACEIs and depression following their prospective cohort study to determine the relationship between BBs and depression as the primary objective. Patients who were newly exposed to antihypertensive medication, including ACEIs, BBs and CCBs, were followed up for six months for new incidences of depression or recurrent depression (Gerstman et al., 1996). Although the results obtained from this study had obvious limitations since they were not adequately adjusted for possible confounders, they presented a comparable rate of depression cases among the three antihypertensive groups indicating that ACEIs may confer no greater or lesser risk than other antihypertensive drug classes. This finding was replicated by a later cross-sectional study conducted by Feng and colleagues (2008), where they demonstrated a null association between ACEIs and depressive symptoms after adjusting for potential confounders (Feng et al., 2008). A Norwegian cross-sectional study investigated the association between the different classes of antihypertensive medications (ACEIs, CCBs, BBs and diuretics) and depressive symptoms in a large sample of 55,472 patients (Johansen et al., 2012). Among the four groups of antihypertensive drugs, the ACEI group showed less frequent depressive symptoms compared to the untreated systemic hypertension group, though with no statistical significance (OR = 0.54, 95% CI 0.28–1.08). In a five-year retrospective study, Williams et al. (2016) followed-up 836 patients for the first depressive episode. They showed that among 80 patients who were on ACEI treatment, the incidence of depression was zero, while among the 756 patients who were not on ACEI, the incidence of depression was 5.3%, suggesting a possible beneficial effect of this class in depression. Boal et al. (2016)

further supported the later suggestion. They examined mood related hospital admissions of 144,660 patients treated with antihypertensive monotherapy for a five-year follow-up. Their results showed that ACEIs and ARBs were associated with the lowest risk of mood disorder admissions comparing to other antihypertensive drug classes. Similar findings were revealed by Kessing et al. (2020) showing that ACEI and ARB associated with decreased risk of depression incident. By contrast, Cao et al. (2019) followed 181,709 newly diagnosed hypertensive patients for four years to detect the first antidepressant prescription as a proxy for depression. The results showed that ACEIs had the second-highest risk of depression among participants in all five main classes of antihypertensive drugs compared to ARBs (HR = 1.35, 95% CI 1.28–1.42).

Recently, it has been suggested that medications targeting the RAS system, including ARBs and ACEIs, may have a beneficial effect as therapeutic agents for mood disorders (Vian et al., 2017). However, even without mentioning the large inconsistencies between the clinical studies, evidence supporting this theory was largely based on early case reports, observational studies that were poorly designed and small trials. More recent data, however, have been published from adequately powered and well-designed clinical studies, although it remains inconclusive, precluding firm conclusions about the efficacy of ACEIs and ARBs for depression.

1.2.9 TZD and TZD related diuretics

TZDs have been considered a cornerstone in the treatment of hypertension since their introduction in 1958 (Moser and Feig, 2009). Apart from the UK, most recent European and American guidelines continue to recommend this class as a first-line treatment for essential hypertriton (McNally et al., 2019). TZDs are also used to manage oedema as a result of HF, hepatic cirrhosis and kidney diseases. They are grouped into TZD and TZD-like diuretics according to their molecular structure. Members of the TZD class derive from benzothiadiazide, while TZD-like diuretics lack this structural derivative, but both groups share a similar mechanism of action. In general, TZDs and TZ-related diuretics exert their BP lowering effect by promoting diuresis through restricting sodium reabsorption and enhancing Na^+ and water excretion. They were specifically designed to inhibit the action of the Na^+/Cl^- co-transported (NCC) at the distall convoluted tubule, where about 7%-10% of the daily filtered NaCl is returned into the circulation (Ives, 2012). The resulting low intracellular Na^+ in turn lowers intracellular Ca^{2+} mediated by the Na^+/Ca^- exchanger (NCX1). This triggers a compensatory mechanism at the proximal tubule that enhances the reabsorption of Ca^{2+} through a passive diffusion into the luminal epithelial cells inducing a hypocalciuric effect. For this reason, TZDs can also be used as a treatment for kidney stones produced by hypercalciuria (Ives, 2012).

1.2.9.1 TZD and depression

Overall, the CNS side effects of TZDs, such as fatigue, confusion and lethargy, are reported to be 5% to 10% (Gengo and Gabos, 1988). Compared to the other four main classes of antihypertensive agents, TZDs show no frequent association with depression and have not been used as a therapeutic agent in this context. One study suggested a link between TZD and depression based on a case series of eight patients (Okada, 1985), though further evidence confirming this finding is lacking. Subsequent studies that have investigated the relation between TZDs and depression have almost consistently reported a null association (Table 1-6) (Boal et al., 2016, Kessing et al., 2020, Pająk et al., 2013, Shaw et al., 2019). A mechanism of action by which TZDs induce a neuropsychiatric complication is

suggested to be through an electrolyte imbalance rather than a direct action on the CNS as they penetrate the BBB in very low concentrations.

Table 1-6 Antihypertensive drugs and risk of depression

Study	Study population	N	EM	FU Yrs	Studies antihypertensive drugs					Index	Effect size
					CCB[1]	BB[2]	ACEI[3]	ARB[4]	DIT[5]		
Cross-sectional studies											
(Agustini et al., 2020)	Hypertensive elderly population	14,195	DS		**-/+**	**+**	**-/+**	**-/+**	NA	**OR**	1.05 (0.92–1.19)[1] 1.37 (1.17–1.60)[2] 1.08 (0.95–1.23)[3] 0.99 (0.89–1.12)[4]
(Dhondt et al., 2002)	Elderly participants	2646	DS		**+**	**+**	**-/+**	NA	NA	**OR**	1.52 (1.05–2.21)[1] 1.33 (1.03–1.72)[2] 1.16 (0.75–1.79)[3]
(Feng et al., 2008)	Elderly participants	2804	DS		**-/+**	**-/+**	**-/+**	**NA**	**-/+**	**OR**	1.07 (0.70, 1.63)[1] 1.01 (0.67, 1.52)[2] 1,56 (0.95, 2.57)[3] 0.92 (0.53, 1.62)[5]
(Johansen et al., 2012)	Healthy participants	55,472	DS		**-/+**	**-/+**	**-/+**	NA	NA	**OR**	1.04 (0.70–1.53)[1] 1.20 (0.78–1.83)[2] 0.54 (0.28–1.08)[3]
(Johnell and Fastbom, 2008)	Elderly participants	732,230	AD		**-**	**-**	**-**	**-**	**-**	**OR**	0.87 (0.86–0.88)[1] 0.87 (0.86–0.89)[2] 0.97 (0.95–0.99)[3] 0.95 (0.93–0.98)[4] 0.77 (0.75–0.79)[5]
(Nasr et al., 2011)	Primary care hypertensive patients	378	AD		**+/-**	**+**	**-**	**-**	**-**	**χ^2(*p-value)***	(0.40)[1] (0.10)[2] (.229)[3] (0.086)[4] (0.016)[5]
(Patten and Lavorato, 2001)	Aged 18 or older who were residents of telephone-containing households	2,542	MDD		**-/+**	**-/+**	**-/+**	NA	NA	**PR**	1.54 (0.86-2.73)[1] 0.71 (0.32-1.58)[2] 0.51 (0.20-1.25)[3]

Study	Study population	N	EM	FU Yrs	Studies antihypertensive drugs					Index	Effect size
					CCB[1]	BB[2]	ACEI[3]	ARB[4]	DIT[5]		
Case-control (cases/controls) and retrospective studies											
(Cao et al., 2019)	Newly diagnosed with HTN	181,709	AD	5	+	+	+	+	+	**OR**	1.16 (1.12-1.21)[1] 1.37 (1.32-1.43)[2] 1.35 (1.28-1.42)[3] 1.17 (1.08-1.27)[5]
(Hallas, 1996)	Prescription database	11,244	AD	3	+	-/+	+	NA	-/+	**RR**	1.31 (1.14-1.51)[1] 1.09 (0.95-1.26)[2] 1.29 (1.08-1.59)[3] 0.90 (0.79-1.02)[4]
(Kessing et al., 2020)	Population-based registry data	3 747190	MDD+AD	10	-	-	-	-	-/+	**HR**	0.96 (0.95–0.97)[1] 0.94 (0.93–0.94)[2] 0.97 (0.96–0.98)[3,4] 1.00 (1.00–1.01)[5]
(Patten et al., 1996)*	Hypertensive hospitalised patients	226/471	DD	-	-/+	-/+	-/+	NA	NA	**OR**	1.09 (0.70-1.71)[1] 0.29 (0.14-0.56)[2] 1.23 (0.82 -1.87)[3]
(Rathmann et al., 1999)	Diabetic patients	972/972	MDD	0.5	+	+	-/+	NA	-/+‡	**OR**	2.2 (1.2–4.20)[1] 2.6 (1.1–7.00)[2] 1.3 (0.8–2.20)[3]
Prospective cohort studies											
(Boal et al., 2016)	Patients in secondary care hospital	144 066	MDD	5	+	+	-	-	-/+	**HR**	2.28 (1.13–4.58)[1] 2.11 (1.12–3.98)[2] (1.56 0.65–3.73)[5]
(Gerstman et al., 1996)	Prescription database	3,782	AD	0.5	-/+	-/+	-/+	NA	NA	**Cases per person-years**	(16.9/1000 p-y)[1] (20.2/1000 p-y)[2] (28.9/1000 p-y)[3]
(Ried et al., 2000)	Hypertensive elderly patients	1 660	AD	2	+	+	-/+	NA	NA	**OR**	1.97 (1.34-2.90)[1] 1.55 (1.08-2.24)[2] 1.14 (0.76-1.73)[3]
(Shaw et al., 2019)	New user of AHT with no previous history of MDD	538 730	AD+MDD	8	-/+‡	+	+	+	-/+‡	**HR**	2.68 (2.45–2.92)[2] 1.17 (1.04-1.31)[3,4]
(Sørensen et al., 2001)	Population-based registry prescription	58 529	Suicide	6	-/+	+	-/+	NA	NA	**SMR**	1.2 (0.80-1.70)[1] 1.6 (1.20-2.10)[2] 1.2 (0.70-1.80)[3]

Abbreviations: AD, antidepressants; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; BB, β-blocker; CCB, calcium channel blocker; DD, depressive disorders; DS, depressive symptoms; FU, follow-up; HR, hazard ratio; MDD; major depressive disorders; OR, odd ratio; PR, Prevalence ratio; RR, risk ratio; SMR, standardised mortality ratio TZD, thiazide diuretics.* Subgroup patients stratified by gender (Female) and age (<45 years) showed P <0.00. ‡ Data not shown. (+) significant increase; (-), significant decrease; (+/-) non-significant findings.

1.3 Summary of literature review and rationale for the present study

1.3.1 Depression and risk of future CVD event

Over the past several decades, there has been notifiable progress in our understanding of the complex networks of interacting pathways linking depression with CVD. Several meta-analyses that have been conducted on this topic have provided robust evidence indicating that depression is an independent risk factor for CVD. However, as previously described (section 1.1.5), early observational studies that examined the association between depression and CVD had poorly adjusted for potential confounders, and therefore their results are likely to be biased, posing threats to the accuracy of the estimated risk. Further, apart from Van der Kooy et al.'s study (2007), the main outcomes of previous meta-analyses were a single subtype of CVD, either CHD or stroke. There are now accumulating numbers of observational studies that have assessed a depression risk in relation to stroke, CHD and HF simultaneously; subsequently, these studies have detected the first outcome of the CVD subtype and provided a separate risk estimate for each outcome. A previous meta-analysis that focused mainly on one outcome failed to provide a full picture of the relation between depression and different CVD subtypes. Thus, it remains unclear whether depression is associated with an excessive risk for a specific subtype or whether it imposes an equivalent risk across different types of CVD. Moreover, most of the previous meta-analyses had pooled the risk estimate from observational studies that had measured depressive symptoms at a single time point and extrapolated the results to lifetime exposure. To overcome this problem and provide more valid estimates for CVD risk attributed to depression, more recently published prospective studies have measured depression at multiple instances over the follow-up time. Therefore, one of the questions that remains to be answered is how changes in depressive symptoms over time may affect the risk of developing CVD and whether the magnitude of risk increases as the number of depressive episodes increases.

Hypertension is the strongest risk factor for CVD (Fuchs and Whelton, 2020), which is the leading cause of morbidity and mortality worldwide. Meanwhile, as an established risk factor for CVD, depression is as important and independent of the classic risk factors. Thus, if these two highly common diseases coexist, they would

have a large and relevant impact on public health and clinical context. A large body of evidence shows pathophysiological overlaps between hypertension and depression and, accordingly, the pathways of commonly used antihypertensives drugs may also play a role in the pathogenesis of depression. Indeed, there has been a long-standing debate on whether antihypertensive drugs are associated with an increased or decreased risk of depression and which of the drug classes are most likely to cause such an effect. Early epidemiological studies conducted on this matter were constrained by methodological limitations, including cross-sectional designs, small sample sizes, short follow-up duration, lack of a control group and inadequate adjustment for potential confounders. Further, the main objective of most previous studies was to look for a relation between a specific drug class of antihypertensive and depression. However, these studies did not clearly enable clinicians to discern how each drug class may impact depression. More recent epidemiological studies have revealed that each class of antihypertensive drug might have a distinct effect on mood disorders. Therefore, as an antihypertensive drug is one of the core medications in a CVD therapeutic plan, it is crucial to determine the exact relation of each individual class with depression and evaluate the possible impact of medication-related factors, such as dosage regimen and duration, on this relation to avoid deleterious consequences.

1.4 **Aim and objectives of the thesis**

This study has two main objectives. First, to conduct an updated systematic review and meta-analysis to assess the association between depression and new-onset CVD event (defined as CHD, stroke and HF) among CVD free patients to answer the following questions:

1- Whether the magnitude of depression risk is similar across different CVD subtypes.

2- How changes in depressive symptoms over time may affect the risk of developing CVD.

The Second objective is to investigate the association between the exposure to the five major classes of antihypertensive agents including CCB, BB, ACEI, ARB and TZD and risk of depression and determine whether there is a dosage relation.

2 Methods

2.1 Systematic review

This section describes the strategies and methods applied to systematically review the association between depression and CVDs. The research methods of this review were performed in accordance with the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup et al., 2000), with reference to the Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocols (PRISMA-P)(Shamseer et al., 2015). The protocol for this review is registered in the open access online registry, PROSPERO, University of York, York, United Kingdom (CRD42018094605) and is available at https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=94605 (See Appendix 1).

2.1.1 Eligibility criteria

The criteria for considering and excluding studies for this review were conducted in accordance with the Population Exposure Comparison Outcome Study design (PECOS) framework (Morgan et al., 2019).

2.1.1.1 Population

Adult men and women aged 18 years old and over, and free of stroke and CHD at study entry. Studies focusing on men and women aged younger than 18 years or with existing CHD or stroke at study entry were excluded from this analysis.

2.1.1.2 Exposure and comparators

The exposure and comparators were evaluated based on the following criteria: (1) the eligible type of exposure is depression, which refers to MDD, clinical depression, depressive disorder and depressive mood; (2) the screening or diagnosis strategies used to measure depression include a valid standard SRS, structured clinical diagnostic interview, physician/clinical diagnosis and/or anti-depressant medication use; (3) depression should be reported as a binary variable by grouping participants by depression status based on the presence or absence of depressive symptoms (yes/no); (4) depression should be assessed and reported

separately if the study examined other mood disorders within the same population; (5) as a measure of the association between depression and the main outcomes (CVDs incidences and/ or CV mortality), an adjusted RR with 95% CI or HR with 95% CI should be reported or at least sufficient information provided to compute effect size 6) eligible studies should have a control group with no depression.

Studies that measured depression combined with other mood disorders, such as anxiety and did not report depression separately, were excluded. Further exclusions included screening or diagnostic strategies that non-specifically measured depression (e.g. measured anxiety alone or other generalised psychological distress), studies that analysed depression as a continuous variable or did not provide enough information to abstract RR or HR, and studies without a control group of participants with no depression diagnosis.

2.1.1.3 **Outcome measures**

Endpoints for decision-making were evaluated based on the following: (1) Outcome: defined as diseases of the circulatory system based on the $10^{th}/11^{th}$ Revision of the ICD-10. In this review, the outcome of interest was divided into three groups: (a) CHD (ICD-10 code I20-I25, or ICD-11 code BA40-BA60), (b) cerebrovascular disease (stroke) (ICD-10 code I60-I69 or ICD-11 code 8B00- 8B03, 8B10, 8B11 and 8B20), and (c) HF (ICD-10 code 150 or ICD-11 code BD10-13, BD1Y and BD1Z). Transient ischemic attack (TIA) has been also considered as part of the stroke outcome (defined by the ICD-10 code G45). (2) Outcome measures: CVD events defined by hospital admission or medical records with diagnoses of CVDs, or death certificates with CVD as underlying cause of death. (3) Type of outcome: Primary outcome is the incidence of CVDs including fatal or non-fatal CVDs observed among depressed individuals compared with those who were free of depression. The following outcome measures were excluded: (1) Outcomes of other CVDs not mentioned in the list of outcomes or (2) a composite CVD endpoint.

2.1.1.4 **Study design**

Studies were included if they met the following criteria: (1) a prospective cohort study design; (2) provided estimates as a measure of the association between depression and the main outcomes– an adjusted RR with 95% CI or HR with 95% CI

should be reported and (3) adjusted for potential confounders or at least for age and gender. Observational studies that had retrospective, case-control, cross-sectional or case series study designs or clinical review papers, letters to the editor and editorials without data were all excluded. Further, studies that did not adjust for potential confounders (age and sex) were also excluded.

2.1.1.5 Language

Only articles written in the English language were considered.

2.1.1.6 Information sources

A comprehensive search strategy was applied to ensure more complete coverage of relevant studies including published and unpublished studies. The search strategy was developed by examining existing systematic reviews on depression as a risk factor for incidence of various heart diseases, to identify relevant electronic database and search terms (Gan et al., 2014, Nicholson et al., 2006, Rugulies, 2002, Van der Kooy et al., 2007, Wu and Kling, 2016).

2.1.2 Search strategy for identifying relevant studies

2.1.2.1 Electronic searching

The search was applied to four databases: Medical Literature Analysis and Retrieval System Online (MEDLINE (OVID), from 2005 onwards), the Excerpta Medica Database (EMBASE (OVID) from 2005 onwards), Psychological Information Database (PsychINFO, from 2005 onwards) and Web of science database from 2005 onwards.

Literature search strategies were developed using medical subject headings (MeSH) and text words related to depression and CVDs, including the following: the umbrella term ‘depress*’ was used to capture all studies that had a title related to depression disorder or depressive symptomatology. ‘Depress*’ was combined with other keywords such as ‘myocardial infarction’, ‘cardiovascular disease’, ‘cardiovascular disorder’, ‘cerebrovascular disease’, ‘cerebrovascular

disorder', 'stroke', 'ischemic heart disease', 'heart failure', 'cohort', 'hyperten*'[1], 'longitudinal' and 'prospective' on human beings.

Table 2-1 shows the search strategy used in more detail. The literature search in the current review spanned the last 15 years because the latest comprehensive systematic review covering depression and CVDs was performed in January 2005 (Van der Kooy et al., 2007).

[1] High blood pressure key words were also included to make the search comprehensive enough to encompass hypertension, the strongest risk factor of CVD for a better understanding of the relation between depression and hypertriton and how the association, if exist, will influence the relationship between depression and CVD and antihypertensive drugs and depression.

Table 2-1 Keywords use for electronic database search

#	Keyword search
1	exp depression/
2	depress*.mp.
3	low mood.mp.
4	depress* symptom*.mp.
5	(symptom* of adj3 depress*).mp
6	major depress*.mp.
7	1 or 2 or 3 or 4 or 5 or 6
8	hypertension/
9	(elevated blood pressure or high blood pressure).mp.
10	hyperten*.mp.
11	blood pressure.mp.
12	8 or 9 or 10 or 11
13	ischemic heart disease/ or angina pectoris/ or coronary artery atherosclerosis/ or coronary artery constriction/ or coronary artery obstruction/ or coronary artery thrombosis/
14	(ischemic heart or cardiac disease*).mp.
15	myocardial infarction.mp.
16	(coronary adj2 disease*).mp.
17	infarc*.mp.
18	or/13-17
19	cerebrovascular disease/ or cerebrovascular disorder/
20	(cerebrovascular disease* or cerebrovascular disorder*).mp.
21	stroke.mp.
22	or/19-21
23	(cardiovascular disease* or cardiovascular disorder*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
24	heart failure.mp.
25	exp cohort studies/
26	cohort*.tw.
27	exp longitudinal study/
28	exp prospective study/
29	cohort.mp.
30	or/25-29
31	(animal$ not human$).sh,hw.
32	30 not 31
33	12 or 18 or 22 or 23 or 24
34	7 and 32 and 33
35	limit 34 to yr="2005 -Current"

2.1.2.2 **Searching other resources**

To ensure literature saturation, screening was performed on the references list of the included studies based on the aforementioned criteria. Previous reviews and meta-analyses were also screened for eligible studies (Barlinn et al., 2015, Dong et al., 2012, Li et al., 2015a, Meng et al., 2012, Nicholson et al., 2006, Pan et al., 2011b, Rugulies, 2002, Van der Kooy et al., 2007, Wu and Kling, 2016).

2.1.3 **Study records**

2.1.3.1 **Data management**

The electronic database citations, studies retrieved from the references list of past reviews and studies retrieved from relevant articles were imported and collated into a reference manager software (Endnote). Endnote X9 was used to manage and delete duplicate records. All imported references from the searched electronic databases in Research Information Systems, Inc. (RIS) or endnote export (.enw) format were then grouped into smart groups labelled according to the source of every reference (MIDLINE, EMBASE, Web of Science and PsychINFO). Then, all references were exported to Rayyan, a screening software, using endnote the export (.enw) output style. Rayyan is a free Web and mobile app designed to speed-up the initial screening of abstracts and titles through a semi-automation process facilitating a rapid exploration and filtering search for eligible articles (Ouzzani et al., 2016). Further identification of duplicates was carried out in Rayyan.

2.1.3.2 **Selection process**

After uploading the citations to Rayyan, screening was performed in two stages: (1) the title and abstracts were screened and (2) all studies that met the inclusion criteria were exported to endnote using the export (.enw) output style. The full text-articles for all titles that appeared to meet the predefined eligibility criteria were then retrieved and screened. As the primary reviewer, I conducted an initial screening of the titles and abstracts of all retrieved articles. The full texts of potentially eligible studies were retrieved and assessed independently for eligibility by two reviewers (myself and Mohammed Ba-zuhair). Any disagreements

between the reviewers were resolved through discussions with the supervising authors (Prof Sandosh Padmanabhan and Prof Daniel Smith).

2.1.3.3 **Data collection process**

Data extraction from all selected articles was carried out by the primary reviewer (Anwar Mansour Alnakhli) (i.e. 100%). Mohammed Ba-zuhair crosschecked all articles for accuracy and independently extracted the data.

2.1.4 **Data extraction**

The data extraction form was designed after considering how much information should be collected. A standardised Microsoft Excel 2010 worksheet was used to extract data from the included studies for assessment of study quality and evidence synthesis.

The extracted study population data included (1) characteristics of the study population at baseline (i.e. mean age in years and percentage of male), (2) overall number of study participants and (3) the health condition of enrolling participants before study entry, including history of CVDs.

The extracted data for exposure were (1) definition of depression (cut-off point), (2) measurement of depression, (3) how frequently depression was measured throughout the study period, (4) whether a study defined a minimum period that depressive symptoms should last to make a proper diagnosis (e.g. for the past two weeks) and (5) type of depressive symptoms assessed by a SRS.

For the outcome of interests, the following data were extracted: (1) main type of outcomes and other subtypes if reported, (2) measurement method of the outcomes and (3) number of cases.

The extracted study design data were (1) name of the first author, (2) year of publication, (3) name of the cohort, (4) study design, (5) study location, (6) duration of follow-up, (7) covariates that were adjusted in the multivariable analysis and (8) most fully adjusted RR or HR with the corresponding 95% CI.

2.1.4.1 Dealing with missing data

When data were missing, the original authors of the study were contacted with a maximum of two email attempts to obtain the relevant missing data. If there was no response, studies with insufficient information were excluded from this review and analysis.

2.1.5 Assessment of methodological quality

To evaluate the risk of bias within eligible studies, the methodological quality of potential studies was assessed using the Newcastle-Ottawa scale (NOS) for cohort studies (Wells et al., 2014). The NOS is a validated eight-item scale for assessing the quality of non-randomised studies in meta-analyses. This scale uses a 'star system', assigning a maximum of nine stars for the eight items. The stars are allocated based on three domains. The first domain refers to the selection of the study groups and assesses four items each worth one star: (a) representativeness of the exposed cohort, (b) selection of non-exposed cohort, (c) ascertainment of exposure, and (d) demonstration that the outcome of interest was not present at the start of the study. The second domain, which is allocated a maximum of two stars, evaluates the comparability of the groups based on the study design or analysis, meaning that either exposed or non-exposed individuals were matched in the design or confounders were adjusted for in the analysis. The third domain allocates a maximum of three stars to evaluate how the study ascertained the outcome. Stars are awarded for the method used to assess the outcome, whether the follow-up was long enough for the outcome to occur and the adequacy of the cohort follow-up regarding titration rate.

Studies were rated as good, fair or low quality for scores of 7-9, 4-6 or 0-3 stars, respectively based on the most common cut-offs score applied in epidemiological studies (Lo et al., 2014). A justification for the judgement of each item is reported in a risk of bias table.

2.1.5.1 Criteria used in the quality assessment of the included studies

The NOS tool often needs to be adapted by the study author commensurate with the review question of interest. Therefore, criteria were set for each assessment item as an indication of what would be considered acceptable to earn a star.

To gain four stars in the first domain, (1) participants should be representative of the general population and not a select group, (2) the non-depressed group should be selected from the same setting as the depressed group, (3) depression should be assessed either by a standardised psychometric tool specifically designed for depression screening or by a structured interview for clinical diagnosis and (4) the study should state that the enrolled participants were free of stroke andCHD at baseline. In the second domain, to earn one star, the cohort should take into account the most important confounders, including age and sex. To gain two stars, the cohort should additionally adjust for at least for five of the following confounders: CVD risk factors (HTN, diabetes mellitus, hyperlipidaemia, obesity, family history of CVD); behavioural risk factors (smoking, alcohol consumption, physical inactivity, medication adherence); other psychological or mental health problems that may also increase the risk of CVD, e.g. (anxiety); and medication abuse. To earn three stars in the third domain, the study outcome should be measured directly or through a review of secure medical records or self-reported scales, and studies should have a minimum follow-up duration of 10 years and a dropout rate of less than 20%. A guidance of how each item defined in order to allocate a star is presented in Table 2-2.

Table 2-2 Criteria for the NOS to allocate stars for the quality of studies (out of 9 stars)

	Criteria	Acceptable (star awarded)	Unacceptable (star not awarded)
Selection	Representative of cohort		
	Selection of non-exposed cohort	Same setting as exposed cohort	Different setting from exposed cohort
	Ascertainment of exposure	A valid psychometric tool for depression screening or a structured clinical interview	Tools that measures general psychological disorder
	Demonstration that outcome of interest was not present at start of study	Stating that patients with stroke or IHD at baseline were excluded from the study.	No statement mentioned
Comparability	Adjusting for most important confounders	Adjusted for age and sex	No adjustment or adjusted only for sex or only for age
	Adjusting for other important confounders	Adjusting for at least any five of the following: hypertension, diabetes mellitus, hyperlipidaemia, obesity, family history of cardiovascular diseases, smoking, alcohol consumption, physical inactivity, medication adherence, psychological disorders, medication use such as anti-depressants and lipid-lowering agent	Adjusting for less than five
Outcome	Assessment of outcome	Secure records or direct measure	Self-reporting
	Was Follow-Up Long Enough for Outcomes to Occur?	10Years	Less than 10years
	Adequacy of follow-up of cohorts	Dropout rate <20%	Dropout rate is ≥20%

2.1.6 Meta-analysis

2.1.6.1 Meta-analysis software

I used RevMan 5 (Review Manager, 2014) to perform the meta-analysis in this review. RevMan 5 is a software recommended for preparing and maintaining Cochrane Reviews developed by the Cochrane Collaboration Group. It is available free for Cochrane authors and academic use.

2.1.6.2 Data synthesis

For this review, data synthesis in RevMan was conducted using a generic inverse-variance approach, as most studies reported their main outcomes as time-to-event data presented as HR 95% CI. I extracted the HR, upper limit and lower limit of CI from all studies reflecting the impact of depression on CVDs and entered them into the RevMan 5 (version 5.3.5) calculator. The calculator automatically computes the natural logarithm of the HR and the standard error (SE) of the natural logarithm for the HR.

2.1.6.3 Choosing between the ifxed effect and the random effect models for meta-analysis

Meta-analyses are based on one of two statistical models the fixed effect model (FEM) and the random effect model (REM). The assumptions under the FEM are that all studies in the meta-analysis share a common effect size and the variation in the effect size from one study to another is only due to sampling error (Borenstein et al., 2010). Therefore, the summary effect size is the estimate of this common effect size. The null hypothesis being tested in this model is that the effect size of each study is zero for a difference or one for a ratio (Borenstein et al., 2010). Distribution of points observed in the meta-analysis indicates sampling error only and can be reduced by assigning weights to each study in the analysis. Under the REM, it is assumed that the true effect size varies from one study to the next, and the studies included in the meta-analysis represent a random sampling of effect sizes (Borenstein et al., 2010). Thus, the summary effect under the REM is the mean of these effects. The null hypothesis under this model is that the mean effect is zero if no difference exists and one for a ratio. The variation between effect sizes in this model can be explained by sampling error and variation in the true effect size across studies. The variation could also be

minimised by assigning weight to each study in the analysis. Given the differences between the two models, it is not always appropriate to conduct the analysis using both FEM and REM. In this review, I assessed whether REF or FEM should be performed to avoid misleading inferences. Ideally, FEM can be used under two conditions: (1) if all included studies in the meta-analysis were functionally identical, meaning that the subject or exposure/intervention was equivalent among the studies, and (2) if all studies used an identical, narrowly defined population whereby the common effect size cannot be generalised to other populations. In this review, there was a minor diversity across the included studies with respect to the methodological approaches used. Additionally, the goal is to compute the summary effect size with the purpose of extrapolating the results to a wide range of scenarios. Therefore, REM was adopted across all analyses to compute the summary effect size. Under the REM, computing a summary effect is based on assigning more weight to studies that yield a more precise estimate of the effect (Borenstein et al., 2010).

2.1.6.4 **Assessment of heterogeneity**

Heterogeneity in a systematic review is defined as any kind of variability between included studies (Borenstein et al., 2010). This variability may be due to clinical diversity (e.g. variability in participants, exposures and outcomes) and/or methodological diversity (e.g. variability in study design). Statistical heterogeneity is a consequence of clinical or methodological variabilities, or both (Higgins and Thompson, 2002, Higgins, 2011).

To determine the extent of variation in the true effect size between studies, tests of heterogeneity were performed. One common test used is the Chi-squared (X^2, or Chi^2), also known as Q-statistic test (Higgins and Thompson, 2002), which tests the null hypothesis that all the included studies share a common effect size. This review considers a *p*-value of <.05 statistically significant for the presence of heterogeneity. The Higgins (I^2) statistic test was also applied to quantify the variability in effect estimates that is due to true heterogeneity rather than chance (sampling error). The I^2 value ranges between 0% (indicates no observed heterogeneity) and 100% (larger values indicate increasing heterogeneity). I^2 can be interpreted as follows (Higgins, 2011):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Significant heterogeneity is typically considered if I^2 is 50% or more. In the presence of statistically significant heterogeneity, one analytical approach is to incorporate it into an REM. The REM does not fix heterogeneity, but it allows for differences in the treatment effect from study to study (Riley et al., 2011) as it assumes that there is a distribution of true effect sizes. Furthermore, heterogeneity is explored with reference to the characteristics of the studies included in the meta-analysis by performing sensitivity and subgroup analysis.

2.1.6.5 **Publication bias assessment**

Failing to include all relevant studies in the meta-analysis because they were not published is known as publication bias. Several tests can detect and/or estimate the impact of publication bias on a meta-analysis. In this review, I used the funnel plot method. The funnel plot is a simple scatter plot of the intervention/exposure effect estimates from individual studies against the standard error (Sterne et al., 2006, Higgins, 2011). The effect estimates of the studies were plotted on the horizontal axis while the measure of standard error was plotted on the vertical axis. The results from the small studies were scattered at the bottom of the graph, and the spread narrowed for the larger studies. In the absence of bias, the studies were distributed symmetrically around the mean effect size, while in the presence of the bias, the model appeared symmetrical at the top (reflecting large studies) and more studies absence (small studies) near the bottom. This approach cannot be used to estimate the extent of the impact of publication bias on the meta-analysis or the effect size in the absence of publication bias.

2.1.6.6 **Sensitivity analysis**

Sensitivity analysis was performed to assess the robustness of the obtained results. The criteria followed for excluding or restricting certain studies are described in

detail in the methods section of each outcome results chapter (Sections 4.2.1 and 5.2.1).

2.1.6.7 Subgroup analysis

Subgroup analyses are typically undertaken to explore possible sources of heterogeneity. Full details on stratification for the subgroup analysis are provided in each outcome results chapter (Sections 4.2.1 and 5.2.1).

2.2 The Cohort study

2.1.7 The Glasgow Blood Pressure Clinic database (GBPC)

2.1.7.1 Study setting and study population

The study population are all patients attending the GBPC (Williamson et al., 2013), which is the largest and the main specialist hypertension clinic in Glasgow providing secondary and tertiary level service to individuals with hypertension from the West of Scotland. Patients are referred to GBPC if their BP is not well-controlled in primary care with at least three drugs, or if there is evidence of high-risk factors such as early-onset hypertension, features of secondary hypertension, or family history of premature CVD. Structured instruments are used to collect data from all patients attending the clinic and are stored electronically in a single computerised database, which contains information on more than 16,000 patients attending the clinic from 1969 until 2011. All patients were treated at the clinic until their BP control was stabilised, with continuing follow-up at the clinic or in primary care. Use of the anonymized database for analyses is approved by the West of Scotland research ethics service of the National Health Service (11/WS/0083).

2.2.1.1 Laboratory and clinical measurements

A structured format was used to enter clinical details for patients including age, gender, the presence of existing CVD, tobacco use (any versus none), body weight, cholesterol level, renal function and family history of hypertension or premature CVD. Method for data collection and prescription was described in detail on previous work

- Blood pressure measurement

  The patient was placed in either a supine or sitting position for five minutes prior to BP measurement. Maintained, and calibrated mercury sphygmomanometers (Accoson Dekamet MK3,UK) were used for reading blood pressure. The tight clothing was removed, and arm was supported at heart level position. The appropriate cuff size was taken. The cuff was inflated above the brachial artery until the pulse disappeared. When the pulse appeared again by deflating the cuff, the SBP was recorded as an estimation. The cuff was then re-inflated to 30 mm Hg over the SBP estimation, a stethoscope was placed and the cuff was deflated at the rate of 2 mm Hg per second. The SBP was recorded when the rhythmic sound appeared, and diastolic blood pressure (DBP) was recorded when the sound disappeared by continuing the deflation. BP measurements were obtained manually two times. Third measurement was taken if the second reading was significantly lower. The mean of the last two measurements were recorded. The difference between the SBP and DBP was defined as pulse pressure. SBP < 140 mm Hg and DBP < 90 mm Hg were the therapeutic target of blood pressure.

- Smoking status

  Specialist nurses or physicians interviewed patients during their first visit to obtain smoking status information. A copy of this information was kept in the case notes as well as transferred to the GBPC electronic database.

- Body weight and hight

  Calibrated weighing machines were used to measure body weight (Seca 955 chairscale). A height stick was used to measure height. Both body weight and hight used to calculate body mass index (BMI). According to the WHO, a BMI equal to or more than 30 kg/m2 defined as obesity. Overweight or pre-obesity defined as a BMI between 25 and 29.99 kg/m2. A BMI between 18.5 and 24.99 kg/m2 defined as an optimal weight.

- Blood samples were collected at baseline and at regular intervals for estimation of routine hematologic and biochemical indices, including renal function tests and cholesterol level. All biochemical investigations were

performed at the Western Infirmary clinical laboratory service on blood samples obtained at the first visit as part of routine screening.

- Family history

  Records of patients who attended the GBPC from 1969 to 2011 were extracted from the database and reviewed. Each patient attending the clinic completed a structured questionnaire on health details of firstdegree relatives (parents and siblings): alive/dead, number of full brothers and full sisters, history of hypertension, myocardial infarction and stroke, age at death, age at heart attack/stroke, and age at diagnosis of hypertension.

- The Charlson comorbidity index score

  The Charlson comorbidity index (CCI) score was defined using the enhanced ICD-9 codes and ICD-10 codes as described in Quan et al. (2005). The CCI score was calculated for the time of study start date using data on all preceding hospital admissions upto 1990. (meaning between 1990 and 2005).

- Renal function

  Estimated glomerular filtration rate (eGFR) was used to evaluate renal function.eGFR was calculated from the baseline serum creatinine values. Modification of Diet in Renal Disease Study Group (MDRD) equation was used to calculate eGFR. The three variable modification were included with serum creatinine values in this equation. These variable are age, race, and sex as shown in equation below (461).

  eGFR= 32788 $\times$ serum creatinine (in μmol/L) $^{-1.154}$ $\times$ age $^{-0.203}$ *(1.212 if black) $\times$(0.742 if female)

  Based to the National Kidney Foundation Kidney Disease Outcomes QualityInitiative (NKFKDOQI) and based on eGFR, kidney function was classified intonormal or 3, 4, and 5 stages (Levey et al., 2003). While a normal kidney was considered as having an eGFR $\geq$ 60 mL/min/1.73 m2, CKD stage 3 was determined if the eGFR was between 30 and 59 mL/min/1.73 m2. The eGFRs between 15−29 mL/min/1.73 m2 and < 15 mL/min/1.73 m2 were considered as CKD stages 4 and 5, respectively.

2.2.2 The Information Services Division database

Pharmacy refill data were obtained from the Prescribing Information System (PIS), an electronic database of all National Health Service (NHS) prescriptions dispensed to individuals across Scotland, which is maintained by NHS National Services Scotland (NSS) (Ahmed et al., 2015) and linked to the hospitalisation using the unique patient Community Health Index (CHI) number. The PIS is created from information supplied by the Practitioner Services Division of the NSS, which is responsible for the processing and pricing of all NHS prescriptions dispensed in Scotland (Ness et al., 2015). Data on private (non-NHS) prescriptions are not routinely collected and were therefore unavailable for analysis; however, as prescription charges were abolished in Scotland in 2011 and the NHS is free at the point of use for the entire population, the relative contribution of these prescriptions is expected to be low.

The PIS contains fields for a variety of metrics, including prescriber and dispenser information (e.g. location and organizational structure) and prescription details (e.g. the name, strength, formulation and cost of the medicine). Data fields included date of dispensation, the class and name of the medicine, and the number of items. Medicines were categorized by both British National Formulary (BNF) subsection and approved name. Antihypertensive drugs were classified as alpha blockers, ACEI, ARB, BB, CCB, centrally acting antihypertensive, non-thiazide diuretic and thiazide diuretic drugs.

The number of items referred to those items processed and paid for under NHS Scotland, excluding those from GP10A (Stock Order) forms and hospital-based prescription forms. Prescription data and outcome data was obtained from the Information Services Division (ISD) Scotland which provided data for all patients attending the Glasgow Blood Pressure Clinic during the period of 31/12/2003 to 31/03/2013. The CHI number had been used to connect the ISD prescription data and the GBPC data including the patient's BP, demographic characteristics and biochemistry results.

- Daily defined dose of antihypertensive and antidepressants drugs

  Data on refilled prescription for patients extracted from the ISD were converted into defined daily dose (DDD) as illustrated below, to enable comparison of different drug classes.

  - The number of days covered by a specific drug in the study period was calculated. Then, the total quantity of the drug dispensed over the study period – was calculated from the number of tablets/capsules dispensed and the strength of each. The DDD for each drug was obtained from the WHO ATC table (WHO, 2020). The total quantity dispensed was converted into total DDD (equal total quantity dispensed/DDD).

Table 2-3presents the extracted information for each eligible patient.

Table 2-3 Extracted data for patients from the GBPC and ISD from Dec 2003 up to Mar 2013

Demographic information	Classification	Coding
Gender	Categorical	Male (1) and female (2)
Year of birth	Continuous	
Risk factors		
SBP and DBP	Continuous	
BMI	Continuous	
Cholesterol	Continuous	
eGFR	Categorical	≥60ml/min and <60ml/min
Smoking status	Categorical	Non-smoker, currently smoker
Comorbidities at baseline for each subject were determined using CCI score	Continuous	No comorbidity (0), having one comorbid condition (1), having more than one comorbid conditions (2)
Antihypertensive and antidepressants drugs		
Drug class	Categorical	ACEI, ARB, CCB, BB, alpha-blocker, diuretics, centrally acting
Commence date		
Prescription dispensation dates		
Daily dosage	Categorical	Based n tertiles (low, moderate and high DDD)
Other data		
• Date of death • Date of hospital admission due to CVD	•	•

BMI, body mass index; CCI, Charlson comorbidity index score eGFR, estimated glomular filtration rate; SBP; systolic blood pressure; DBP, diastolic blood pressure;

2.2.3 Statistical analysis and packages used for cohort analysis

2.2.3.1 Statistical package

Microsoft Excel 2016, and IBM SPSS statistics 26.0 were used for data analyses.

2.2.3.2 Summary of statistics

Categorical data was summarised using counts and percentage. Whereas continuous data was summarised using median and standard deviation (SD).

2.2.3.3 Comparison of categorical data

A chi-square (X^2) test was carried out to assess the associations of the categorical data. The chi-square (X^2) test for trend was performed to evaluate the linear relationship between the ordered variables (i.e. CCI categories and DDD) and the outcomes. Significance was set at $P<0.05$.

2.2.3.4 Comparison of continuous data

Continuous variables were examined using the Students' T-test, which was applied for comparing the mean of two groups, and the one-way analysis of variance (ANOVA), which was used to compare means of more than two groups. The normality of the continuous data was tested visually (Normal Q-Q plot and histogram) and statistically (Shapiro-Wilk test).

2.2.3.5 Survival analysis

Survival analysis was performed using the Kaplan-Meyer univariate analysis to determine the risk of incident depression among different classes of antihypertensive drugs. A log-rank test was used to compare depression rate between antihypertensive drugs classes. Cox proportional hazards models were used to perform multivariate analysis and coefficients were reported as HR and 95%CI.

2.2.3.6 Generalised estimating equation (GEE)

The GEE was also used to examine the relation between antihypertensive drugs and risk of depression. GEE is a type of general linear model used for clustered data which adjusts for the within-subject correlation present among repeated observations over time (Liang and Zeger, 1986). This test was performed to analyse data of patients on antihypertensive polytherapy by treating each newly introduced antihypertensive drug as a cluster data for each subject. In this context each newly introduced antihypertensive drugs was considered as a repeated admission for each patient. To determine which of the antihypertensive drugs is independently associated with developing depression, a univariate and a multivariate binary logistic model were constructed that simultaneously included all antihypertensive drugs and coefficients were reported as OR and 95%CI.

As there was no control group (i.e. non-users of antihypertensive drugs), the reference group in both analyses (i.e. Cox regression and GEE analysis) investigating the association between different antihypertensive drug classes and incident of depression was determined based on the total number of participants. The ACEI group contains the largest number of participants compared to the other antihypertensive groups and was therefore set as the reference group.

3 Depression and Risk of CVDs: Systematic Review – Screening, Eligibility and Quality Assessment

3.1 Aim

This chapter describes the results of the systematic review search for cohorts studying depression and risk of CHD, stroke and HF. The following sections present the literature search, excluded and included studies, and risk of bias.of the included cohorts.

3.2 Results of the search

As shown in Figure 3-1, the initial search for published studies was carried out from January 2005 to October 2017 using four databases and updated in July 2020. Overall, 21,779 citations and/or abstracts were screened for eligibility. Of these, just over 97% (21,193) were excluded based on the title or abstract, as pre-determined by this review's PECOS criterion. The full texts of the remaining 586 publications were assessed for eligibility. Of these, 467 were excluded and the full texts of the remaining 120 articles were further assessed.

Finally, 32 cohorts were included in this review and 30 were included in the meta-analysis. All included studies were full-length articles except for one study, which was a conference abstract (Sico et al., 2018). Sections 3.2.1 and 3.2.2 describe the details of the excluded and included studies, respectively.

3.2.1 Description of the excluded studies

Overall, 88 cohorts were excluded after screening their full texts for eligibility. Table 3-1 presents the reasons for exclusion for each cohort. Fourteen studies were excluded for different reasons Twenty-two studies had an outcome of interest that was a composite of cardiovascular events, 14 studies did not provide information about whether participants were with stroke and/or CHD at study entry, and 26 enrolled participants with CVD at baseline.

3.2.2 Description of the included studies

This review included 31 studies and 47 reports (Table 3-2). All included studies used a prospective cohort design to investigate the association between depression and the outcomes of interest, which are stroke, CHD and HF. A description of the characteristics of the included studies is supplemented in an individual outcome chapter of the results section (Chapter 4 for stroke outcome, chapter 5 for CHD outcome and chapter 6 for HF outcome).

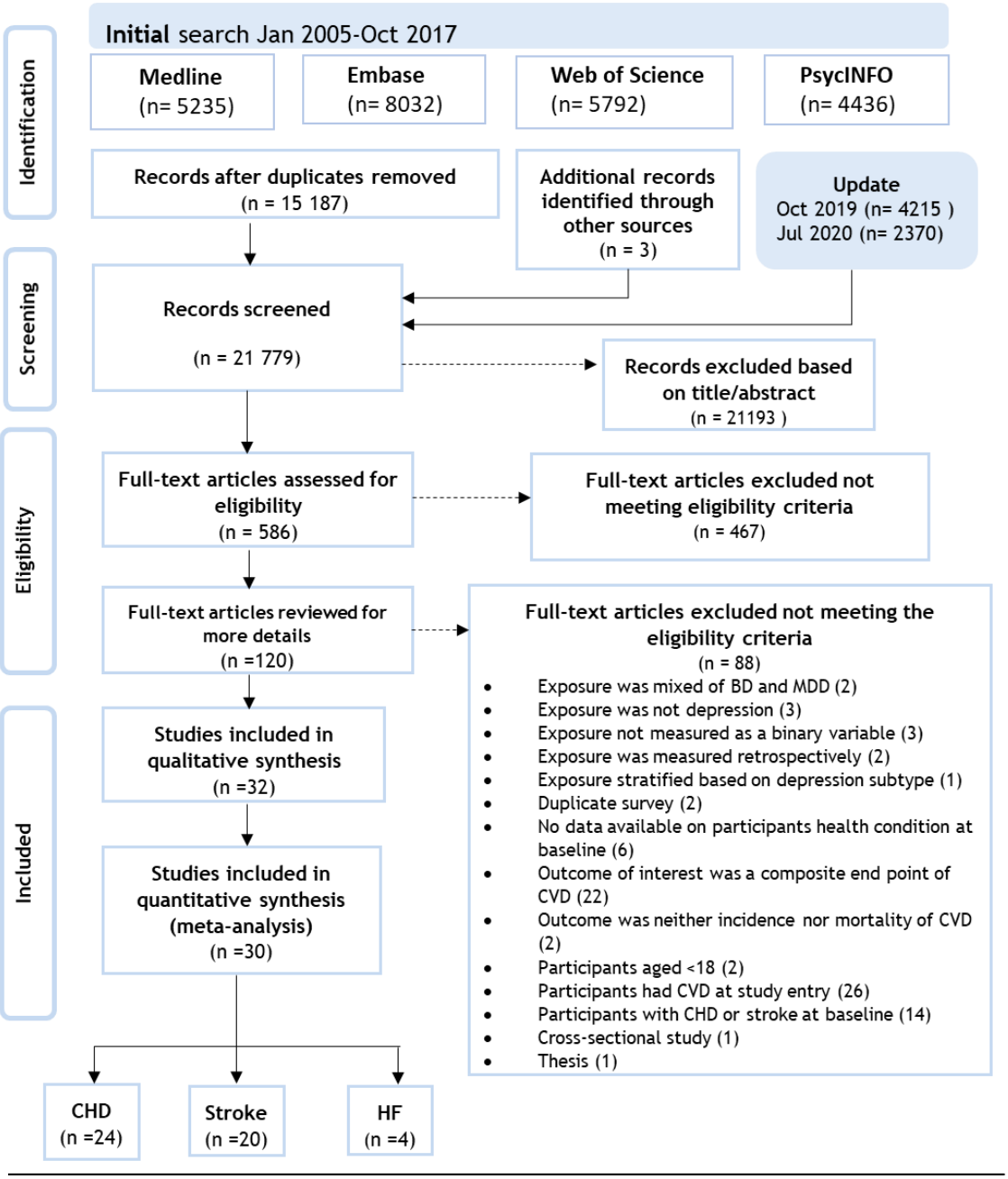

Figure 3-1 PRISMA study flow diagram
BD, bipolar depression; CHD, coronary heart diseases; CVD; cardiovascular diseases; HF; heart failure; MDD, major depressive disordere.

Table 3-1 Reason for exclusion of cohorts

Reference	Elaboration
(Ahto et al., 2007)	Participants with CHD or stroke at baseline
(Almas et al., 2019)	Outcome of interest was a composite end point of cardiovascular event
(Almeida et al., 2019)	Participants had CVD at study entry
(Appleton et al., 2013)	Outcome of interest was a composite end point of cardiovascular event
	Participants had CVD at study entry
(Avendano et al., 2006)	Participants had CVD at study entry
(Azevedo Da Silva et al., 2014)	Outcome of interest was a composite end point of cardiovascular event
(Batty et al., 2014)	Exposure Not depression
(Berecki-Gisolf et al., 2013)	Outcome of interest was a composite end point of cardiovascular event
(Bos et al., 2008)	Participants had CVD at study entry
(Boyle et al., 2006)	Participants with CHD or stroke at baseline
(Burns et al., 2013)	Participants with CHD or stroke at baseline
(Canoui-Poitrine et al., 2017)	Exposure measured as a continuous variable
(Case et al., 2018)	Outcome was a composite end point of cardiovascular event
(Chi et al., 2014)	Participants had CVD at study entry
(Chichetto et al., 2019)	Outcome of interest was a composite end point of cardiovascular event
(Cho et al., 2019)	A Duplicate survey
(Choi et al., 2014)	Outcome of interest was a composite end point of cardiovascular event
(Azevedo Da Silva et al., 2015)	Participants had CVD at study entry
(Deschênes et al., 2020)	Outcome of interest was a composite end point of cardiovascular event
(Egeberg et al., 2015)	Participants had CVD at study entry
(Egeberg et al., 2016)	Participants had CVD at study entry
(Egede et al., 2005)	Participants had CVD at study entry
(Gaspersz et al., 2018)	Outcome was not incidence of CVD
(Gillespie et al., 2019)	No data available on participants cardiac health condition at baseline
(Gilsanz et al., 2017)	Participants had CVD at study entry
(Gilsanz et al., 2015)	Participants had CVD at study entry
(Glymour et al., 2010)	Participants had CVD at study entry
(Goldstein et al., 2015)	Outcome of interest was a composite end point of cardiovascular event
(Gromova et al., 2007)	No data available on participants cardiac health condition at baseline
(Graham et al., 2019)	Participants with CHD or stroke at baseline
(Haaf et al., 2017)	Participants had CVD at study entry
(Hamano et al., 2015)	Participants had CVD at study entry
(Hamieh et al., 2020)	Outcome of interest was a composite end point of cardiovascular event
(Haukkala et al., 2009)	Outcome of interest was a composite end point of cardiovascular event
(Haukkala et al., 2013)	Outcome of interest was a composite end point of cardiovascular event
(Hawkins et al., 2014)	A duplicate survey
(Hazuda et al., 2019)	Outcome of interest was a composite end point of cardiovascular event
(Henderson et al., 2013)	Participants had CVD at study entry
(Higueras-Fresnillo et al., 2018)	Exposure Not depression

Reference	Elaboration
(Hiles, 2015)	Outcome of interest was a composite end point of cardiovascular event
(Huang et al., 2013)	Participants with CHD or stroke at baseline
(Jackson and Mishra, 2013)	Participants had CVD at study entry
(Jackson et al., 2018a)	Exposure Not depression
(Jakobsen et al., 2008)	Exposure mixed of Bipolar and unipolar depression
(Forouzanfar et al., 2016)	Participants had CVD at study entry
(Joyce, 2015)	Thesis
(Kamphuis et al., 2006)	Depression not measured as a binary variable
(Kawada, 2017)	Woring publication type
(Khodneva et al., 2019)	No data available on participants cardiac health condition at baseline
(Klabbers et al., 2009)	Participants aged < 18 years
(Köhler et al., 2013)	Participants had CVD at study entry
(Kouvari et al., 2019)	Outcome of interest was a composite end point of cardiovascular event
(Kubzansky et al., 2006)	Depression was not measured as a binary variable (categorical classification)
(Langvik, 2015)	Participants with CHD or stroke at baseline
(Lankarani and Assari, 2016)	Outcome of interest was a composite end point of cardiovascular event
(Lee et al., 2008)	Participants with CHD or stroke at baseline
(Li et al., 2012)	Participants with CHD or stroke at baseline
(Liebetrau et al., 2008)	Participants had CVD at study entry
(Liu et al., 2016)	Depression measured retrospectively
(Marzari et al., 2005)	Participants had CVD at study entry
(May et al., 2014)	No full data available on risk of CVD
(Mittag and Meyer, 2012)	No data available on participants cardiac health condition at baseline
(Nabi et al., 2010b)	Outcome of interest was a composite end point of cardiovascular event
(Nicholson et al., 2005)	Participants had CVD at study entry
(Norton et al., 2020)	Outcome of interest was a composite end point of cardiovascular event
(O'Brien et al., 2015)	Participants with CHD or stroke at baseline
(Ortega et al., 2017)	Outcome of interest was a composite end point of cardiovascular event
(Pan et al., 2011a)	Participants had CVD at study entry
(Patten et al., 2009)	Participants were aged <18 years old
(Polanka et al., 2018)	Outcome of interest was a composite end point of cardiovascular event
(Poole and Jackowska, 2019)	No data available on participants cardiac health condition at baseline
(Poole and Steptoe, 2020)	Exposure was mixed of depression and inflammatory biomarker
(Pössel et al., 2015)	Participants with CHD or stroke at baseline
(Rantanen et al., 2020b)	Exposure was stratified by depression subtypes
(Rowan et al., 2005)	Participants with CHD or stroke at baseline
(Rutledge et al., 2009)	Participants had CVD at study entry
(Salaycik et al., 2007)	Participants had CVD at study entry
(Scherrer et al., 2015)	Outcome of interest was a composite end point of cardiovascular event
(Seldenrijk et al., 2015)	Outcome of interest was a composite end point of cardiovascular event
(Sims et al., 2015)	Participants with CHD or stroke at baseline
(Sun et al., 2013)	Participants had CVD at study entry
(Sun et al., 2016b)	Depression measured retrospectively

Reference	Elaboration
(Surtees et al., 2008b)	Participants with CHD or stroke at baseline
(Tully et al., 2015)	Outcome was not incidence of CVD
(Vaccarino et al., 2007)	Participants with CHD or stroke at baseline
(Wiehe et al., 2006)	Study design (cross-sectional)
(Xiang and An, 2015)	Outcome of interest was a composite end point of cardiovascular event
(Zahodne et al., 2017)	Participants had CVD at study entry

Table 3-2 Name of included cohorts, main studies outcomes and summary of studies quality

Study	Nama of cohort	Outcome			NOS evaluation		
		CHD	Stroke	HF	Selection	Comparability	Outcome
(Brown et al., 2011)	NA	✓			***	**	**
(Brunner et al., 2014)	The Whitehall study	✓	✓		*	*	***
(Daskalopoulou et al., 2016)	The Cardiovascul-ar research using Linked Besposoke studies and Electronic Health Records (CALIBER)	✓	✓	✓	****	**	**
(Davidson et al., 2009)	The Coronary Artery Risk Development in Young Adults (CARDIA) study	✓			***	**	***
(Everson-Rose et al., 2014)	The Multi-Ethnic Study of Atherosclerosis (MESA)		✓		***	**	**
(Gafarov et al., 2013)	The WHO MONICA-psychosocial (MOPSY) Programme	✓	✓		**	*	***
(Gump et al., 2005)	The Multiple Risk Factor Intervention Trial (MRFIT)	✓	✓		**	**	***
(Gustad et al., 2013)	The Nord-Trøndelag Health (HUNT) study	✓			***	**	**
(Gustad et al., 2014b)	The HUNT study			✓	***	**	**
(Hamieh et al., 2019)	The GAZEL cohort (GAZEL stands for *GAZ* and *ELectricité*)	✓			**	**	**
(Janszky et al., 2010)	NA	✓			***	**	**
(Jee et al., 2019)	National Health Insurance Service (NHIS) Database of Korea	✓	✓		****	**	**
(Karlsen et al., 2020)	The Osteoporotic Fractures in Men (MrOS) study	✓	✓		**	**	**
(Khambaty et al., 2016)	The Veterans Aging Cohort Study (VACS)	✓			***	**	**
(Krishnan et al., 2005)	NA		✓		**	**	**
(Ladwig et al., 2006b)	Multinational MONItoring of trends and determinants in CArdiovascular disease (MONICA)	✓			***	**	**
(Li et al., 2012)	Nationwide National Health Institute (NRI) Databse of Taiwan		✓		****	**	**

Study	Nama of Cohort/Database	Outcome			NOS evaluation		
		CHD	Stroke	HF	Selection	Comparability	Outcome
(Li et al., 2019)	China Health and Retirement Longitudinal Study (CHARLS).		✔		****	**	**
(Majed et al., 2012)	Prospective Epidemiological Study of Myocardial Infarction (PRIME) Study	✔	✔		**	**	***
(Mathur et al., 2016)	The East London Primary Care Database	✔	✔		***	**	***
(Mejia-Lancheros et al., 2014)	PREvención con DIeta MEDiterránea (PREDIMED)	✔	✔		***	**	*
(Moise et al., 2016)	Reasons for Geographic And Racial Differences in Stroke	✔	✔		***	**	**
(Nabi et al., 2010a)	Health and Social Support study (HeSSup)	✔	✔		***	**	*
(Péquignot et al., 2016)	Three City Study	✔	✔		***	**	**
(Rahman et al., 2013)	The Screening Across the Lifespan Twin Study (SALT) Interview	✔	✔		****	**	*
(Rajan et al., 2020)	The Prospective Urban Rural Epidemiological (PURE)	✔	✔	✔	****	**	**
(Scherrer et al., 2011)	The Veterans Health Administration (VHA) Database	✔			***	*	*
(Sico et al., 2018)[a]	Veterans Aging Cohort Study (VACS)		✔				
(Whang et al., 2009)	The Nurses' Health Study (NHS)	✔			**	**	*
(White et al., 2015)	Veterans Aging Cohort Study (VACS)			✔	***	**	*
(Wouts et al., 2008)	Longitudinal Aging Study Amsterdam (LASA)		✔		***	**	**
(Wulsin et al., 2005)	The Framingham Heart Study (FHS) original and offspring cohort	✔			***	**	**

CHD, coronary heart diseases; HF, heart failure; NOS, New castle-Ottawa Scale; [a] Conference abstract

3.3 Discussion

3.3.1 Depression screening tools

3.3.1.1 The validity of screening tools and the cut-off scores used to identify depression cases

As several types of SRS instruments are available for depression screening, the most suitable one should be selected based on the evidence-based literature about these assessments, especially regarding their intended use and appropriate populations. The cohort studies included in this review used various types of validated SRS for depression screening (Table 3-3). In the following section, I describe and identify tool performance for depression screening and the optimal cut-off score commonly used to identify depression cases based on the best evidence available in the literature.

The 20-item CES-D scale is among the most widely used SRS to measure depressive symptoms (Carleton et al., 2013); The scale has high levels of validity and reliability to detect both clinical depression (defined by DSM criteria) and subthreshold depression within a wide range of populations (Andresen et al., 1994). The original 20-item CES-D scale has a score ranging from 0 to 60 and patients are categorised into one of the following four groups: not depressed (0–9 points), mildly depressed (10–15 points), moderately depressed (16–24 points) and severely depressed (more than 25 points). A cut-off score of 16 or higher is recommended as an optimal score to identify depression cases (Andresen et al., 1994). Most of the studies included in this review that used the CES-D scale used the original 20-item version and a cut-off point of 16 to classify persons as having ‘depressive symptoms’. Davidson et al. (2009) and Gump et al. (2005) used lower cut-off scores (10 and 13 respectively) to identify individuals with depression, which may have resulted in overestimating the number of depression cases and increasing the number of false positives of depression. Li et al. (2019) used the 10-item CES-D, a short version of the original scale, with a cut-off score of 12 indicating elevated depressive symptoms. The CES-D 10 has excellent screening properties for MDD, particularly in older adults, and has sufficiently identified depressive cases as those diagnosed by clinician (Irwin et al., 1999). Irwin et al. (1999) recommended a cut-off score of 4 for older individuals. However, evidence

shows that a higher score such as 12 would be more appropriate for different population including elderly (Baron et al., 2017, Björgvinsson et al., 2013). The cohort by Moise et al. (2016) used a 4-item short version of the CES-D. The 4-item CES-D asks whether patients over the past week (1) felt depressed, (2) felt lonely, (3) had crying spells, and (4) felt sad, which corresponded with items 6, 14, 17 and 18 on the original version. This shortened version with a cut-off point of 4 was validated in a heterogeneous community population of 411 women who were at high risk of contracting and transmitting human immunodeficiency virus (Melchior et al., 1993). The 4-item CES-D was found to correlate (r= 0.89) with the full CES-D version. Recently, researchers have questioned the validity and psychometric properties of several items on the CES-D, including item number 17 (i.e. 'I had crying spells') (Carleton et al., 2013). Previous studies suggest robust sex differences in response to item 17 due to cultural norms regarding emotional expression rather than true differences in depressive symptoms, leading to potentially invalid cut-off scores, an overestimation of women's CES-D score and an underestimation of men's scores (Carleton et al., 2013, Rivera-Medina et al., 2010). Given that the Moise et al. (2016) cohort was 41.2% male and the validity of 4-item CES-D has only been assessed among female population, this study may not have accurately captured depression in the sample.

Majed et al. (2012) reported that depression was assessed using the 13-item modified CES-D, and the fourth quartile was used to identify depression cases. This study used data from the Prospective Epidemiological Study of Myocardial Infarction (PRIME); a review of the original protocol indicates that the PRIME study used a 13-item modification of the Welsh depression subscale which derived from the Minnesota Multiphasic Personality Inventory (Empana et al., 2005, Sykes et al., 2002).

The 21-item BDI is a multiple-choice inventory used widely to assess the level of depressive symptoms in adults. Each item is scored from 0 to 3 points, giving a total score in the range of 0-63. The scale was constructed in 1961 and has since been employed in numerous empirical studies (Beck et al., 1961). The internal consistency of this tool has been confirmed by several studies in psychiatric and non-psychiatric samples and, on average, they report alpha-coefficients higher than 0.75 (Richter et al., 1998). Further, the BDI has good content validity, as it reflects six of the nine DSM-III criteria for major depression (Moran and Lambert,

1983). Previous studies have suggested that the range of scores from 0 to 9 can be considered normal (Kendall et al., 1987). The Centre for Cognitive Therapy distributed the following guidelines for BDI cut-off scores: a score of < 10 indicates none or minimal depression; 10-18 indicates mild to moderate depression; 19-29 indicates moderate to severe depression; and 30-63 indicates severe depression (Beck et al., 1988). The appropriateness of the BDI cut-off scores depends on the nature of the sample and the purpose for which the instrument is being used (Beck et al., 1988). For example, if the purpose is to include the maximum number of depressed cases, then the cut-off score is lowered to minimise false negatives. However, if 'pure' depressive cases are included, then a higher cut-off score is used to minimise false positive (Beck et al., 1988). In this review, Nabi et al. (2010a) used the 21-item BDI screening tool to define depression cases with a BDI cut-off score of 10, which includes even mild cases of depression.

The General Health Questionnaire (GHQ) (Goldberg, 1972) was developed as a general measure of psychiatric disorders and common mental health problems including depression, anxiety, somatic symptoms and social withdrawal (Jackson, 2007). The reliability coefficients of the GHQ range from 0.78 to 0.95 in various studies (Jackson, 2007). The original version of the GHQ contains 60 items (GHQ-60) covering four main areas: depression, anxiety, social performance and somatic complaints. Other short versions are available that include 12, 28 or 30 items. Brunner et al. (2014) used existing data from the Whitehall II cohort, an occupational study, to examine the impact of depression on the incidence of CHD and stroke. Depression was assessed using the 30-item GHQ (Stansfeld and Marmot, 1992). Theoretically, the GHQ-30 removes all questions related to somatic symptoms and captures the remaining three factors: depression, anxiety, and social performance; this version is perceived to be a stronger measure of psychological symptoms and can be used when circumstances demand, with only slight penalties in reliability and validity (Goldberg, 1972). The main concern with Brunner et al. (2014) study is that it used a nonspecific screening instrument for a common mental disorder, capturing depressive symptoms as well as anxiety, which is not the focus of my review. The study further measured depression using the 20-item CES-D scale and reported a moderate agreement between the two screening tools. The performance of 30-item GHQ were also tested against the revised Clinical Interview Schedule, which is a valid measure of mental disorders

as a criterion for detecting a depressive episode; the findings showed a sensitivity of 0.78 (0.40–0.96) and a specificity of 0.83 (0.78–0.87), which are reassuring of the ability of GHQ to detect depression cases in their cohort (Head et al., 2013).

One study used the 15-item Geriatric Depression Scale (GDS) with a cut-off score of 5 to identify depression cases in an older population (Krishnan et al., 2005). The GDS was the first depression screening tool designed specifically to identify late-life depression in older people (Yesavage et al., 1982). The original version comprised 30 items with a yes/no format and a cut-off of 10 indicating depression cases (Yesavage and Sheikh, 1986). A shorter version of 15 items (cut-off score of 5) was developed and validated against the original 30-item version and the DSM-III criteria for depression. The 15-item version can be successfully used as a screening device for depression in the elderly (Yesavage and Sheikh, 1986), with specificity and sensitivity scores of 79%–100% and 67%–80%, respectively (Watson and Pignone, 2003).

Whang et al. (2009) used the 5-item Mental Health Index scale (MHI-5) with a cut-off score of 52 to identify depressed individuals. This tool is a subscale of the Short-Form 36 Health Status Survey designed to capture psychological distress versus wellbeing (Ware et al., 1993). The survey was originally constructed from the long version of the 38-item MHI, and it includes one or more items from each of the four major mental health dimensions: depression, anxiety, loss of behavioural/emotional control and psychological wellbeing (Ware et al., 1993). Although the MHI-5 scale is not specific to depression it performs better as a measure of depression than as a measure of these other disorders (Cuijpers et al., 2009, Rumpf et al., 2001, Thorsen et al., 2013). The MHI-5 has been shown to have high sensitivity and specificity for major depression, with an area under the receiver-operating characteristic curve of 0.88 to 0.91 for the detection of mood disorders or major depression (Berwick et al., 1991). The MHI-5 scale is scored from 0 to 100, with lower scores indicating more depressive symptoms. No optimal cut-off score was used for predicting depressed cases (Hoeymans et al., 2004, Strand et al., 2003). Some authors have recommended a cut-off score of 52 (Holmes, 1998), whereas others recommend a score of 60 (Rumpf et al., 2001). Overall, the literature shows that the MHI-5 has good performance at this cut-off score of 52 for detecting major depression (Berwick et al., 1991, Holmes, 1998).

Ladwig et al. (2006b) assessed depressed symptomatology using the DEpression and EXhaustion subscale (DEEX scale). This scale combines eight items (fatiguability, tiredness, irritability, loss of energy, difficulty concentrating, inner tension, nervousness, anxiety) rated from 0 to 3, leading to a score of 24. Clinically, the DEEX scale identifies symptoms of reduced vitality, weakness and 'vital exhaustion', but without the assessment of negative self-concept and feelings of guilt; it is thus used as a proxy for measuring depression in a large population-based epidemiological study but is not limited to major depressive disorder. Ladwig et al. (2006b) reported that the internal consistency of the subscale was high (Cronbach's alpha = 0.88). In their cohort, the cut-off score was derived statistically where subjects in the top third of the depressive symptom distribution were considered the index group with depressed mood Ladwig et al. (2006b), (Ladwig et al., 2006a).

Two cohorts in this review conducted by the same authors used the 14-item Hospital Anxiety and Depression Scale (HADS) (Gustad et al., 2013, 2014b). The HADS is a well-recognised assessment instrument comprising 14 items – 7 measuring depression and 7 measuring anxiety (Zigmond and Snaith, 1983). It has good concurrent validity, performing well as a psychiatric screening device (Bjelland et al., 2002, Lipman, 1982) and has been shown to have acceptable psychometric properties. The depression subscale in the HADS emphasises anhedonia and excludes somatic items. Items are scored on a 4-point scale, ranging from 0–3; the higher the score, the greater the depression and anxiety (each subscale ranges from 0-21). There is no single generally accepted cut-off score for the HADS and choosing between the score ranges depends on the intended use of the scale. In the original study, two cut-off scores for depression subscales were suggested: 8-10 for possible and 11 or more for definite cases of depression (Zigmond and Snaith, 1983). The latter score is likely to produce the best result with one false positive and no false negatives (Zigmond and Snaith, 1983). Gustad et al. presented the HR results for the two score ranges (8-10 and ≥11) and I extracted the HR for participants scoring ≥11 on the HADS to include only those patients with a high probability of suffering from depressive symptoms (i.e. a low proportion of false positives).

Evidence suggests that there tend to be no major differences in performance among depression screening tools (Siu et al., 2016). Accordingly, no single SRS is

recommended over another, and the most practical one for the clinical setting can be used (Alexopoulos et al., 2014, Siu et al., 2016). Some authors recommended using both observer-rating scales, such as the Hamilton Rating Scale for Depression and Montomery–Asberg Depression Rating Scale, in addition to an SRS for a complete assessment of depression (Uher et al., 2012). In addition to the variability in the screening tools, the time frame of the questions also varies between tools. For a depressive episode, a minimum duration of two weeks is required for a diagnosis following the gold standard criteria (ICD-10 and DSM-IV) (NICE, 2009), although shorter durations may also be reasonable if the symptoms are unusually severe (WHO, 1993). In this review, the SRS tools measured depressive symptoms each within a certain time frame (i.e. today, past week, past weeks and past month) (Table 3-3). The validity of these differences in the recall period for depressive symptoms has not yet been examined in the general population (Maske et al., 2015). Further, as shown in Table 3-3, the SRS used by cohorts in this review differ widely in the symptoms they ask about. As previously mentioned, symptoms of depression are composed of different categories involving somatic, cognitive and affective symptoms (see Section 1.1.3). However, some SRS more dominantly focus on one or another category. For example, in the Gustad et al cohort, depression subscale in the HADS emphasises anhedonia (a subset of affective symptoms) and excludes somatic items. The 13-item subscale modified from the Welsh focuses solely on affective symptoms. The 10-item short version of the CES-D focuses predominantly on somatic symptoms, while the 4-item CES-D predominantly focuses on affective symptoms. The GDS excludes somatic symptoms and focuses on cognitive and affective symptoms. Among the 19 cohorts, only few studies justified the use of the selected SRS (Gustad et al., 2014b, Karlsen et al., 2020, Krishnan et al., 2005). In this section, I do not intend to discuss the type of symptoms addressed by each tool and its suitability for the targeted population in each cohort, as this is beyond the scope of my research. This information is included only to present the symptoms heterogeneity between studies which can exert a significant impact on identifying depression cases and determining the severity of depressive symptoms as they depend on gaining scores on the SRS.

Table 3-3 Summary table of the depression screening instruments used by the included cohorts

Instrument used	K	Specifically measures depression	Content	Time frame of questions	Score range	common cut-off score	Cut-off score used in this review	Refrence
20-item BDI	1	Yes	Cognitive, affective, somatic and vegetative symptoms	Today	0-63	10	10,16	(Nabi et al., 2010a)
20-item CESD	9	Yes	Positive affect, negative affect, somatic problem, activity level, and interpersonal items		0-60	16	16,25	
10-item CESD	1		Three items on negative affect, five items on somatic symptoms, and two on positive affect	Past week				(Li et al., 2019)
4-item CESD	1		Negative affect			4	4	(Moise et al., 2016)
DEEX sub-scale	1	No	Fatigability, tiredness, irritability, loss of energy, difficulty in concentrating, inner tension, nervous-ness, anxiety symptoms	Not reported	0-24	-	Third tertiles	(Ladwig et al., 2006b)
30-item GHQ	1	No	Common mental health problems/domains of depression, anxiety, somatic symptoms and social withdrawal	Past few weeks	0-30	4	4	(Brunner et al., 2014)
15-item GDS	1	Yes	Affective and cognitive symptoms common in elderly	Past week	0-15	5	5	(Krishnan et al., 2005)
5-item MHI	1	No		Past month	0-100	No optimal cut-off point-	52	(Whang et al., 2009)
13-item modified subscale of the Welsh depression subscale derived from the Minnesota Multiphasic Personality Inventory	1	Yes	Negative perceptions of life (e.g. 'I feel helpless')	Not reported	0-13	No predefined cut-off point	Fourth quartile vs First quartile	(Majed et al., 2012)
15-item MONICA-psychological Interview depression scale	1	Yes	Not reported	Not reported	0-15	Not reported	Not reported	(Gafarov et al., 2013)
14-item HADS	1	Yes	Anhedonia symptoms	Past week	0-21	7,8 or 10,11	8	(Gustad et al., 2013, 2014b)

BDI, Beck Depression Inventory; CES-D, Centre for Epidemiologic Study Depression Screen, DEEX, DEpression and EXhaustion subscale; GHQ, General Health Questionnaire; GDS; Geriatric Depression Scale; K, number of studies; MHI, Mental health Index scale; MONICA, Multinational Monitoring of Trends and Determinants of Cardiovascular Disease

3.4 NOS for assessment of the quality of included cohort studies

A full description of the NOS instruments and how stars awarded for each study are summarised in chapter2 (section 2.1.5). From the 31 cohort studies, around 60% (20) of the studies were considered good and 30% (10) were fair. One was not assessed because it was an abstract (Sico et al., 2018). Figure 3-2 presents the results of the 30-study quality analysis by domain. The major drawbacks were identified in the selection and outcome assessment. The following section describes the quality of the studies based on each domain of the NOS. Justification for how each studies has been evaluated is presented in Appendix 2.

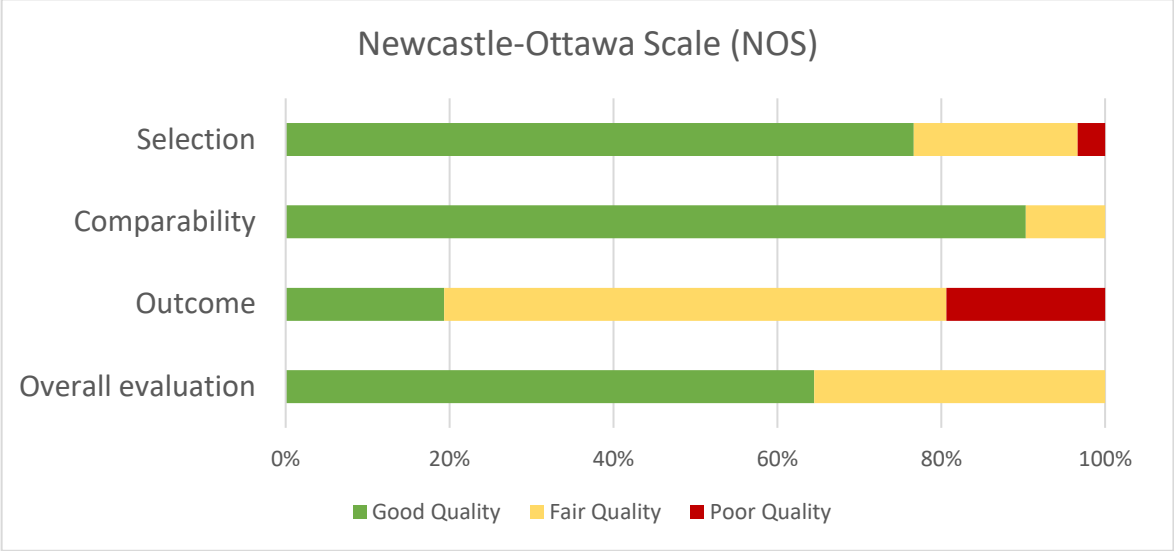

Figure 3-2 Results from the Newcastle-Ottawa risk assessment tool for cohort studies
It presented the results for each domain as well as the overall evaluation of the 30 cohort studies included in this review

3.4.1 Selection

3.4.1.1 Representativeness of the exposed cohort

Thirteen studies had sampled cohorts that were conducted among selected group of particpants (Brunner et al., 2014, Gafarov et al., 2013, Gump et al., 2005, Janszky et al., 2010, Karlsen et al., 2020, Khambaty et al., 2016, Krishnan et al., 2005, Majed et al., 2012, Mathur et al., 2016, Mejia-Lancheros et al., 2014, Scherrer et al., 2011, Whang et al., 2009, White et al., 2015), while the remaining studies were represented to the general population and each therefore gain one star.

3.4.2 Selection of the non-exposed cohort

As all included studies drew their exposed and non-exposed groups from the same population, all of them are awarded one star for this domain.

3.4.2.1 Ascertainment of exposure

In this domain, star allocation is restricted to studies that used medical records or structured interviews to identify the exposure which was 12 studies.

3.4.2.2 Demonstration that the outcome of interest was not present at the start of the study

Under this domain, it is sufficient for a study to report a clear statement defining their population to be free of both stroke and CHD before study entry to earn a star. This is regardless of the method used to assess the participant's medical history. In my review, apart from Brunner et al. (2014) and Gump et al. (2005), all included studies defined their population to be free of stroke and CHD at baseline with a clear statement either by using medical records or self-reported questionnaires; therefore, each earned a star. However, for Brunner's and Gump's studies, I relied on a previous meta-analysis (Barlinn et al., 2015) because the authors performed an additional analysis that included studies with participants free of cardiac diseases. Accordingly, I assumed that these two cohorts had excluded patients with stroke and CHD at baseline, and I therefore assigned a star to each.

3.4.3 Comparability

In this domain, a maximum of two stars could be allocated. Comparability assesses cohorts based on the design or analysis. Confounders are divided into two categories, as shown below, and each category merits one star.

3.4.3.1 Adjusting for most important confounders

As stated in the method (section 2.1.5.1), age and gender were potential confounding variables. Cohort studies had to adjust for both age and gender to be allocated a star. All cohorts were awarded a star for this category.

3.4.3.2 Adjusting for additional confounders (a second important factor)

Studies that adjusted for at least five of the previously mentioned additional confounders (section 2.1.5.1) earned a star. Only three studies did not adjust for these confounders (Brunner et al., 2014, Gafarov et al., 2013, Scherrer et al., 2011).

3.4.4 Outcome

3.4.4.1 Assessment of outcome

In this domain, the allocation of stars depends on the method used to confirm outcome occurrence. Blind, independent assessment, reference to secure records and linkage to medical records were considered acceptable assessment methods to earn a star. Apart from Li et al. (2019) and Rajan et al. (2020), all included studies reported the outcome using these criteria and were thus all awarded one star.

3.4.4.2 Sufficient follow-up duration for outcomes to occur

An acceptable length of follow-up was set at 10 years. Eleven studies had a follow-up duration less than this period (Li et al., 2012, Li et al., 2019, Mejia-Lancheros et al., 2014, Moise et al., 2016, Nabi et al., 2010a, Rahman et al., 2013, Scherrer et al., 2011, Sico et al., 2018, Whang et al., 2009, Wulsin et al., 2005, White et al., 2015), but the remaining cohorts were each awarded one star.

3.4.4.3 Adequacy of follow up of cohorts

In this domain, the follow-up of the exposed and non-exposed cohorts was assessed to ensure that losses were unrelated to either the exposure or the outcome. One star was assigned to cohorts that achieved complete follow-up for their subjects or if the proportion lost to follow-up was less than 20%. Eight studies stated that follow-up was completed for 100% of their participants and each were allocated one star (Gafarov et al., 2013, Majed et al., 2012, Mathur et al., 2016, Davidson et al., 2009, Gump et al., 2005, Jee et al., 2019, Krishnan et al., 2005, Ladwig et al., 2006b). Five studies reported a small proportion of lost to follow-up (<20%) and were allocated one star each (Gump et al., 2005, Moise et al., 2016, Pequignot et al., 2013, Wulsin et al., 2005, Rajan et al., 2020). The remaining cohorts did not provide any proportion or description of those lost to follow-up.

3.5 Discussion

This chapter describes the protocol for identifying studies used in this systematic review and discusses the main methodological challenges that might explain the high diversity observed between the included studies.

Many studies in this review have issues that may introduce bias, leading to an underestimation or overestimation of the true effect of exposure. The NOS is an easy and convenient instrument recommended by the Cochrane Collaboration to assess the risk of bias in observational studies (Reeves BC et al., updated March 2011). Further, I chose this tool because it would be easier to compare my assessment with previous reviews in this area that had used the same instrument (Barlinn et al., 2015, Gan et al., 2014, Wu and Kling, 2016).

The first item in the NOS tool assesses the representativeness of the cohort's population. About 30% of the included cohorts were not representative of the general population as they were conducted on selected groups of patients. This means that important baseline imbalances probably existed across studies and can be considered a potential source of bias. However, the NOS tool defined the representativeness of the cohort with respect to the community, meaning that even enrolling a group of patients that is unrepresentative of the general population but still representing their community is sufficient to meet this

criterion. Nevertheless, doing so might affect the exposure-outcome association since there is a high chance that some factors associated with the selection also determine the outcome of interest (Pizzi et al., 2013). The impact of selecting individuals that are not representative to the general population can be observed in Scherrer et al. (2011) study, which showed that the risk of future CHD is significantly high among patients with a high risk, such as diabetic patients, compared to those without.

Further, a valid ascertainment of exposure based on the NOS can occur via secure records or a structured interview. The psychiatric field is different from other medical areas, as the diagnostic process relies exclusively on clinical evaluation (Luchini et al., 2017). Therefore, it is important to determine whether a study identified cases through a structured interview or an SRS. Although the two methods showed moderate to strong agreement, an SRS is likely to be affected by the patient's interpretation of the questions and their cultural conception of depression. Additionally, not all aspects of depression can be self-assessed (Sartorius et al., 1986). In this review, approximately 60% (n = 19) of the included studies had a potentially inadequate measure of depression, as they used an SRS to identify cases. On balance, the nature of depression makes it difficult to diagnose and distinguish it from other psychological disorders, even when using the 'gold standard' diagnostic criteria. Other psychiatric illness, particularly BD, may also be mistakenly diagnosed as depression (Hantouche et al., 1998, Smith et al., 2011). These issues could all affect the risk estimate in this review in either direction, leading to an under- or overestimation of depression risk.

The second item in the NOS tool relates to the comparability of cohorts, which is based on study design and analysis. In this review, 90% of the studies (n = 28) were awarded the maximum score (2 stars) for this item despite the idiosyncratic list of adjustable covariates. However, awarding the maximum score does not necessarily mean that those studies had properly adjusted for the relevant covariates. It has been suggested that determining an appropriate set of covariates is important because it can help to reduce the risk of bias in observational studies (Steiner et al., 2010). I prepared a comprehensive list of what I considered the 'most important covariates' in the protocol based on my knowledge and what I have read in the literature. However, it is recommended that this step be done with the assistant of subject-matter experts to ensure only

related covariates were adjusted for (Bero et al., 2018). Frasure-Smith and Lesperance (2005) summarised studies linking depression and cardiac disease and proposed that the majority of studies failed to explain the reasons behind their choice of covariates and that the variables selected were idiosyncratic, making comparisons of the adjusted outcomes difficult. In addition, some crucial covariates considered to be a risk factor for the outcome of interest were not measured; thus, residual confounding cannot be ruled out, which may therefore contribute to finding a positive association between depression and incident CVD. For example, family history of premature CHD is a well-known risk factor for CHD incidence (Schildkraut et al., 1989, Snowden et al., 1982) and recently it has also been suggested as a risk factor for depression incidence (Khandaker et al., 2019). In this review, of the 22 studies examining the association between depression and CHD, only three (Janszky et al., 2010, Mejia-Lancheros et al., 2014, Whang et al., 2009) adjusted for this risk factor. The same problem applies to studies examining the relationship between depression and stroke. A recent case-control study found that low physical activity was the most important risk factor, accounting for 59.7% of all strokes (Aigner et al., 2017). Nevertheless, this covariate was rarely considered by studies examining the relationship between depression and stroke (Everson-Rose et al., 2014, Majed et al., 2012, Karlsen et al., 2020, Moise et al., 2016).

The selection of covariates is one of the main issues when studying the association between depression and CVD because the positive relation is, in some cases, a bidirectional relation between depression and some classical risk factors, such as hypertension, diabetes and obesity (Pan et al., 2010, Rotella and Mannucci, 2013, Pan et al., 2012, Skilton et al., 2007), making it difficult to determine whether depression is an independent risk factor for CHD and stroke. Carney and Freedland (2017) and Penninx (2017) previously discussed this kind of challenge in relation to the association between depression and CHD. Hypertension is a good example of the covariate selection challenge in the depression-stroke relation. A summary meta-analysis suggested that depression increases the risk of hypertension incidence (Meng et al., 2012). At the same time, hypertension is one of the most important established risk factors for stroke, accounting for 27.1% of all strokes (Aigner et al., 2017). Accordingly, it is possible to include hypertension as a covariate in the predictive model, but it might mediate rather than confound the

association between depression and stroke. Thus, the scenario would be as follows: depression as the first exposure may lead to hypertension, which in turn leads to the earlier development of stroke. In this case, covariate adjustment for hypertension would be inappropriate because this covariate would be on the causal pathway between depression and stroke. In a matched cohort study, Li et al. (2012) followed 5,015 participants, who were free of metabolic syndrome and stroke at the study entry, for nine years. The authors found that a large proportion of depressed patients suffered from major comorbidities, most frequently hypertension, before stroke onset and thus concluded that a history of clinical depression would not directly increase the risk for stroke, but rather acted indirectly through known stroke risk factors such as metabolic diseases. However, it is unlikely that this completely explains the increased stroke risk, as the results are rather consistent across studies examining the association between depression and stroke, even after excluding hypertensive patients (Gafarov et al., 2013).

The third item in the NOS tool relates to the outcome of interest, which includes three domains. The second domain is whether the follow-up duration was long enough for the outcome to occur. I selected a cut-off point of 10 years as an acceptable length of follow-up, but that was based on past reviews (Barlinn et al., 2015, Li et al., 2015a). Further, the average length of follow-up in the stroke and CHD review was around 12 years. Thus, I have tried to see the effect of depression on the average follow-up period of the included studies.

Authors using the NOS assessment tool can develop and apply their own criteria and assign different quality scores for the same study. Indeed, there was a low agreement and considerable diversity in the overall quality score when comparing my evaluation to the previous reviews using the same tool (Barlinn et al., 2015, Gan et al., 2014, Wu and Kling, 2016) and none described their detailed criteria used to assess the risk of bias. A sensitivity analysis can be done to investigate the impact of study quality on the effect size. However, the scoring approach is subjective and a study with a high score does not necessarily mean that it is high quality. Thus, a sensitivity analysis based on study quality was not performed to avoid obtaining a misleading conclusion.

4 Depression and risk of incident stroke: An updated systematic review and Meta-analysis

4.1 Introduction

4.1.1 Stroke prevalence and burden

Overall, the incidence of stroke is declining worldwide, although it remains one of the leading causes of death globally in the last 15 years (World health Organisation, 2018). In 2016, the GBD provided a systematic review analysis of the global, regional and national burden of stroke from 1990 to 2016 regarding prevalence, incidence, deaths, years lived with disability, years of life lost and disability-adjusted life-years (DALYs) (G.B.D. Stroke Collaborators, 2019). According to this report (G.B.D. Stroke Collaborators, 2019), there were around 80 million prevalent cases of stroke and 13.7 million new stroke cases globally in 2016. Of the total number of prevalent strokes, an average of 84.4% (82.1%–86.4%) were ischaemic. The prevalence of stroke cases was slightly higher in women (41.1%) than in men (39.0%). Between 1990 and 2016, a decline in the age-standardised incidences was reported in most regions globally, with the largest decreases in Latin America. The number of deaths due to stroke and the age-standardised DALY rates for stroke reduced by 36.2% and 34.2%, respectively, over the same period. Despite these improvements, it was recorded that stroke accounted for 5.5 million deaths globally and remained the second largest cause of death after CHD in 2016 (G.B.D. Stroke Collaborators, 2019). Several risk factors contribute to the increased risk of stroke, most of which are modifiable. An international case control study of 3,000 stroke patients found that the majority of strokes (90%), particularly ischemic stroke, can be explained by 10 risk factors (O'Donnell et al., 2010): hypertension, current smoking, waist-to-hip ratio, diet risk score, lack of physical activity, alcoholism, cardiac disease, diabetes mellitus, psychosocial stress and depression, and ratio of apolipoprotein B to A1. Depression based on this report accounted for a 35% (OR 1.35, 1.10–1.66) increased risk of stroke.

4.1.2 Stroke and depression: A bidirectional link

The association between depression and stroke is well established and is considered bidirectional, although it is unclear how each condition acts as a risk factor for the other.

4.1.2.1 Depression in stroke patients

Depression is one of the most common psychiatric disorders occurring in stroke survivors (Chemerinski and Robinson, 2000). A systematic review and a meta-analysis comprising 61 studies demonstrated that 3 out of 10 stroke survivors are likely to manifest depressive symptoms (Hackett and Pickles, 2014). In stroke patients, depression as a complication may exert a significant negative impact on stroke recovery and impair outcomes, resulting in significant disability (Paolucci et al., 2019), increased mortality and lower quality of life (Ayerbe et al., 2013). According to the meta-analysis by Ayerbe et al. (2013), which examined studies published up to 2011, the pooled prevalence of depression among stroke patients at any point after stroke was 29% (95% CI, 25–32). The researchers attempted to identify the major risk factors predicting post-stroke depression stroke (PSD), and they concluded that in addition to stroke severity, pre-stroke depression and cognitive impairment are associated with PSD (Ayerbe et al., 2013).

4.1.2.2 Depression and risk of stroke

The association between depression and risk of stroke incidence is well established. The first meta-analysis to detect an association between depression and stroke was conducted by Van der Kooy et al. (2007). Pooled data from 10 observational studies before 2005 revealed that depression is associated with a 43% (OR 1.43, 1.17-1.75) increased risk of new stroke onset, but with significant heterogeneity among the studies (Van der Kooy et al., 2007). Many other studies were subsequently conducted, which have been summarised in four detailed meta-analyses (Barlinn et al., 2015, Dong et al., 2012, Li et al., 2015a, Pan et al., 2011b). The most recent meta-analysis pooled data from 28 studies and revealed an increased risk of an incident stroke for depression by 40% (overall RR 1.40, 95% CI, 1.27–1.53; p = .0001) (Barlinn et al., 2015). Description and main limitations of these previous reviews were discussed in section 4.5.7 of this chapter. Briefly,

most past reviews enrolled patients with a history of stroke and/or CHD; thus, the association between depression and stroke may arise due to reverse causation. Although evidence suggests that the effect of depression on cardiac diseases and stroke is independent of the presence of either disease since the aetiologies are likely to be different (Widimský et al., 2013), evidence also suggests that cardiac diseases moderate the association between depression and stroke (Wouts et al., 2008). This suggestion is logical, given that the prevalence of vascular risk factors are high in cardiac patients and they therefore have a greater burden of subclinical cerebrovascular diseases that in turn may increase the possibility of residual confounding in longitudinal cohort studies (Barlinn et al., 2015). Additionally, the past reviews have evaluated the association between baseline depression and stroke incidents, assuming without confidence that this prospective relation is stable over a long duration. Therefore, I aimed to update and expand the prior knowledge of the depression-stroke relation by performing a systematic review and meta-analysis of cohort studies.

4.1.3 **Aim**

This chapter conducts a systematic review and reports the meta-analysis of prospective cohort studies that have examined the effect of depression on the risk of stroke in individuals with no known history of stroke or CHD.

4.1.4 **Hypothesis**

1- Depression is associated with an increased risk of overall stroke incidence.

2- Depression increases the risk of first-ever stroke in a dose-response manner.

3- Baseline depression predicts future stroke as well as depression measured on a multiple instant.

4.2 Methodology

4.2.1 Search strategy and selection criteria

Chapter 2, Section 2.1 provided a full description of the methods used for this systematic review and meta-analysis, and Chapter 3 described risk of bias of the studies included in this review.

4.2.2 Statistical analysis and data synthesis

HR was used as the parameter of interest to study the association between depression and stroke. One study used OR to report the estimated risk (Krishnan et al., 2005) and was excluded to maintain consistency across studies. One study provided HRs for women and men separately (Majed et al., 2012) and I pooled both risk estimates using the FE model to obtain one overall estimate for the primary analysis. Two studies provided more than one stroke outcome (i.e. outcomes divided by stroke subtypes) (Daskalopoulou et al., 2016, Majed et al., 2012), and one provided HRs for stroke in relation to different measures of depression (e.g. using self-reported scales [SRS] or clinical interviews). In these cases, I only pooled HRs that corresponded with the largest number of events to obtain a study level HR for the primary analysis. Other reports were included in subgroup analysis.

4.2.2.1 Data synthesis

I performed sensitivity analysis by first excluding the studies by Gump et al. (2005) and Mejia-Lancheros et al. (2014) because, although the study populations were free from CVD at baseline, they had a high cardiovascular risk. In addition, I excluded the study by Rahman et al. (2013) because it used an early version of the ICD (ICD-7), which used a broad classification of depression that was different from the definition of MDD in later versions of ICD. I also excluded the studies by Brunner et al. (2014) and Gafarov et al. (2013) because they reported only demographic-adjusted HR and did not adjust for other health-related confounders, as previously discussed in section 2.1.5. I restricted the analysis to studies that excluded incident stroke cases in the first year of follow-up (Brunner et al., 2014, Majed et al., 2012, Pequignot et al., 2013, Rahman et al., 2013) to minimise reverse causality. I also restricted the analysis to include studies that

measured depressive symptoms at multiple instances over the follow-up period and modelled depression as a time-dependent variable in Cox's proportional hazard model (Everson-Rose et al., 2014, Moise et al., 2016, Wouts et al., 2008, Péquignot et al., 2016). Furthermore, I restricted the inclusion criteria to include only studies that evaluated incident stroke and CHD as their primary outcomes and provided a separate risk estimate for each. Finally, I examined the influence of a single study on the overall risk estimate by excluding one study and combining the remainders in turn (one-study-removed meta-analysis). I also performed subgroup analyses to investigate the heterogeneity and to determine whether the effect of depression varied with different characteristics of studies and the included participants in the following groups: (1) type of depression assessment stratified based on SRS, clinical diagnosis, antidepressants combined with clinical diagnosis and antidepressants alone; (2) age 65 and older or below 65; (3) studies with follow-up of less or more than 10 years; (4) stroke subtypes including fata/non-fatal stroke or IS; and (5) studies where participants were free of CHD or free from CHD and other CVD conditions; (6) sample size and (7) study location.

4.3 Results

The findings below are based on 20 cohort studies enrolling 3,154,290 participants, with an average follow-up of 11.2 years (ranging from 4 to 24 years). Nineteen of these studies were included in the quantitative synthesis.

Table 4-1 summarises the details of the 20 studies included in this review, including the first author's, location, sample size of the cohort, proportion of male, mean of age or age range of study population (where applicable), duration of follow-up, measurement method of depression, main outcome, method used to identify the outcome, number of incident cases registered during the follow-up period in both exposed and unexposed groups and variables included in the final adjusted model. The study carried out by Daskalopoulou et al. (2016) was the largest study in this review with nearly 2 million participants (1,937,360), followed by that of Mathur et al. (2016) with 524,952 participants. The majority of the included cohort studies (10 studies) were conducted in Europe, followed by five in the U.S, three in Asia and one was a multinational study. Most of the studies recruited females and males, either in equal or different proportions, with the

exception of four studies. The cohort examined by Gafarov et al. (2013) was exclusively female, while those of Gump et al. (2005), Majed et al. (2012) and Karlsen et al. (2020) included only males. The mean or median age of participants varied across all studies, with five studies targeting elderly populations (Karlsen et al., 2020, Krishnan et al., 2005, Mejia-Lancheros et al., 2014, Péquignot et al., 2016, Wouts et al., 2008). The diagnosis of depression was largely based on SRS (n = 9), with CES-D being the most commonly used assessment scale (n = 7). Screening for depressive symptoms in seven studies was based on clinical diagnosis that originated from a direct evaluation through healthcare professionals according to ICD or DSM criteria (Krishnan et al., 2005, Li et al., 2012, Mathur et al., 2016, Mejia-Lancheros et al., 2014, Rahman et al., 2013, Rajan et al., 2020, Sico et al., 2018). One of the three remaining studies used both SRS and clinical diagnosis (Wouts et al., 2008) and the other two included antidepressant medication as a component of the depression definition in addition to a clinical diagnosis (Daskalopoulou et al., 2016, Jee et al., 2019). Most of the studies reported the outcome either as a composite or single endpoint of fatal or non-fatal ischemic or haemorrhagic stroke (n = 11). Three studies captured different stroke types (ischemic, haemorrhagic and TIA) (Daskalopoulou et al., 2016, Everson-Rose et al., 2014, Jee et al., 2019) and two restricted the endpoint to ischemic stroke (Rahman et al., 2013, Sico et al., 2018). The number of incident stroke cases observed during a total follow-up was reported by all studies except two (Sico et al., 2018, Wouts et al., 2008). Adjustment for confounders was mostly consistent across studies. Apart from Brunner et al. (2014) and Gafarov et al. (2013), all cohorts adjusted for most of the prespecified confounders previously described in Chapter 2 (see Section 2.1.5).

Table 4-2 shows the selected characteristics of interest extracted from the individual studies, comprising the type of population, frequency of measuring depression over the study period, whether the study excluded incident stroke cases that occurred in the first years of follow-up, and the proportion of participants lost to follow-up during the study. On the whole, the studies defined their population as free of stroke and IHD at baseline. However, nine studies extended this definition to exclude individuals with other CVD subtypes *a priori* or in additional analyses (Daskalopoulou et al., 2016, Everson-Rose et al., 2014, Jee et al., 2019, Li et al., 2019, Mejia-Lancheros et al., 2014, Moise et al., 2016,

Rahman et al., 2013, Sico et al., 2018, Rajan et al., 2020). Five studies made frequent assessments of participants' depression status during the study period (Brunner et al., 2014, Everson-Rose et al., 2014, Moise et al., 2016, Péquignot et al., 2016, Wouts et al., 2008), while the remaining studies relied on the baseline assessment only. Six studies excluded incident stroke cases that occurred in the first years of follow-up (Brunner et al., 2014, Jee et al., 2019, Majed et al., 2012, Nabi et al., 2010a, Péquignot et al., 2016, Rahman et al., 2013); however, one had not reported the data (Nabi et al., 2010a) and another study provided HRs for combined stroke and CHD outcomes (Péquignot et al., 2016). Seven studies examined the relation between depression severity and risk of stroke (Brunner et al., 2014, Everson-Rose et al., 2014, Gump et al., 2005, Jee et al., 2019, Li et al., 2012, Nabi et al., 2010a, Péquignot et al., 2016). In terms of attrition rate, six studies did not lose any patients during the study follow-up period (Gump et al., 2005, Jee et al., 2019, Krishnan et al., 2005, Majed et al., 2012, Mathur et al., 2016, Nabi et al., 2010a), four studies reported patients lost to follow-up at a rate of 0.1% to 8% (Brunner et al., 2014, Moise et al., 2016, Péquignot et al., 2016, Rajan et al., 2020), and ten studies failed to report the proportion of loss to follow-up (Daskalopoulou et al., 2016, Everson-Rose et al., 2014, Gafarov et al., 2013, Karlsen et al., 2020, Li et al., 2012, Li et al., 2019, Mejia-Lancheros et al., 2014, Rahman et al., 2013, Sico et al., 2018, Wouts et al., 2008).

Table 4-1 Characteristics of the included cohort studies

study	Location	N	Men (%)	Age (years)	Length of follow-up (years)	Exposure measure	Outcome	Outcome measure	Cases (n)	Confounder adjustment
(Brunner et al., 2014)	EU	10,036	67.2	44.4	24 years 1985-2009	GHQ-30≥ 5	F/NF IS and HS	Self-reported confirmed be using medical records, GP confirmation and death certificate (ICD-9 codes 430–438 or ICD-10 codes I60–I69).	168	Age, sex, and ethnicity
(Daskalopoulou et al., 2016)	EU	1,937,360	54.8	47.5	13 years 1997-2010	Medical records of CD and/or prescription of AD	F/NF IS, HS and TIA	Medical records (ICD-10 codes I60–I69).	21433	Age, sex, smoking, SBP, diabetes, cholesterol, and socio-economic status
(Everson-Rose et al., 2014)	US	6,749	47	62.1	12 years 2000-2012	20-item CES-D ≥16	F/NF IS, HS and TIA	CD (ICD-9 codes 430-438))	195	Age, race, sex, education and study site, SBP, alcohol use, smoking status, moderate and vigorous physical activity, BMI, height, use of anti-hypertensives, diabetes/fasting blood glucose status, HDL- cholesterol, and triglycerides
(Gump et al., 2005)	US	11,216	100	46	18.4 years	20-item CES-D ≥16	F/NF IS and HS	Death certificates According to the ICD-9 codes	167	Age, intervention group, race, educational attainment, smoking at baseline and visit 6, trial averaged SBP, alcohol consumption, and fasting cholesterol, as well as the occurrence of nonfatal cardiovascular events during the trial
(Gafarov et al., 2013)	EU	560	0	25-64	16 years 1995-2010	15-item MOPSY (subscale depression) questionnaire	F/NF IS and HS	Medical records and death certificates	35	Age

study	Location	N	Men (%)	Age (years)	Length of follow-up (years)	Exposure measure	Outcome	Outcome measure	Cases (n)	Confounder adjustment
(Jee et al., 2019)	Korea	481 355	54.15	52.8	13 years 2002-2013	≥ 1 out-patient visit diagnosed according to (ICD-10 codes F32-F33) or prescription of AD at >3 out-patients visits	F/NF IS and HS	Mediacl records (ICD-10 codes I60-I69), divided into IS and HS	17102	Age, smoking status, HTN, hypercholesterolaemia, diabetes and chronic renal failure
(Karlsen et al., 2020)	US	3135	100	76.38	12 years 2003-2015	9-item GADS ≥2	F/NF IS, HS and TIA	Tri-annual questionnaire and/or phone conformed by medical records. Fatal event adjudicated by death certificate, hospital record or next of kin interview. The adjudicators were certified cardiologist	219	Age, education, race/ethnicity, diabetes, antidepressant use, BMI, cholesterol/oxidised LDL, smoking status, drinking habit, physical activity and sleep quality
(Krishnan et al., 2005)	US	110	31	84.4	10 years 1992-2002	GDS-15 ≥6 evaluated by physician according to DSM-III	F/NF IS and HS	Physician diagnoses	24	Age, Sex, level of education, marital status, Mini-Mental State Examination, BMI, HTN, CHF, arterial fibrillation, diabetes, hyperlipidaemia, and smoking
(Li et al., 2012)	China	5015	36.3	≥18	9 years 2001-2009	CD by psychiatrist (according to ICD-9)	F/NF IS and HS	Hospital records	150	Age, sex, diabetes mellitus, HTN, hyperlipidaemia, substance comorbidities
(Li et al., 2019)	China	12417	49.2	58.4	4 years 2011-2015	10-item CES-D ≥12	F/NF IS and HS	Self-reported	190	Age, sex, residence, marital status, educational level, smoking status, drinking status, BP,BMI; history of diabetes, HTN, dyslipidaemia, chronic kidney disease; use of anti-hypertensive medications, diabetes medications, and lipid-lowering therapy

study	Location	N	Men (%)	Age (years)	Length of follow-up (years)	Exposure measure	Outcome	Outcome measure	Cases (n)	Confounder adjustment
(Majed et al., 2012)	EU	9,601	100	55	10 years 1991	Fourth quartile of 13-item-modified CES-D compared with first quartile	F/NF IS and HS	Hospital or general practitioner records according to the WHO MONICA criteria	136	Age, study centres,socioeconomic factors (marital status, education level, employment status) physical activity, smoking status, daily alcohol intake, SBP, use of anti-hypertensive drugs, BMI, total and HDL- cholesterol, treatment for diabetes, and use of antidepressant treatment
(Mathur et al., 2016)	EU	524,952	52.8	35.9	10 years 2005- 2015	CD, read code used in general practice across the UK	F/NF IS and HS	CD Read code used in general practice across the UK	987	Age, sex, and ethnic group, diabetes, HTN, hyperlipidaemia, and smoking anti-depressant prescribing at baseline, obesity, and Townsend deprivation score, presence of co-morbid anxiety
(Mejia-Lancheros et al., 2014)	EU	7,263	42.5	67	7 years 2003-2010	Self-reported and further confirmed in clinical records according to DSM-IV or other mental health scales BDI	F/NF IS and HS	Regular contacts with participants and/or families, annual revisions of medical records, data from GPs, and consultation of the National Death Index	136	Age, sex, smoking, alcohol consumption, BMI, HTN, type 2 diabetes, dyslipidaemia and family history of premature CHD, and type mediterranean diet intervention
(Moise et al., 2016)	US	22,666	41.2	63.9	9 years 2003-2012	4-item-CES-D ≥4	F/NF IS and HS	Self-administered questionnaires with retrieval of medical records, death certificate and autopsy report	663	Age, sex, region, income, health insurance, education, and traditional CHD risk factors (SBP, total cholesterol, HDL- cholesterol, medication use (aspirin, statins, any antihypertensive medications), BMI, albumin: creatinine ratio, diabetes mellitus, pack-years of cigarette smoking, self-reported alcohol use, physical inactivity, medication adherence, high-sensitivity C-reactive protein, antidepressant use, QT interval corrected for heart rate, atrial fibrillation and left ventricular hypertrophy

study	Location	N	Men (%)	Age (years)	Length of follow-up (years)	Exposure measure	Outcome	Outcome measure	Cases (n)	Confounder adjustment
(Nabi et al., 2010a)	EU	23, 282	41	20-54	7 Years 1998-2005	21-item-BDI ≥10	F/NF IS and HS	Hospital discharge register or mortality reports based on (ICD-10 codes I60-169)	129	Age, sex, education, alcohol consumption, sedentary lifestyle, smoking, obesity, HTN or diabetes and incident CHD or incident CBVD
(Péquignot et al., 2016)	France, EU	7,313	36.6	≥65	10 years	20-item CES-D ≥16	F/NF IS and HS	Self-reported further confirmed by medical reports, interviews with the patient's physician or family, death certificates and autopsy reports. All possible event were adjudicated by three independent expert committees	245	Age, gender, city, education level (>12 years), living alone, current smoking,>3 glasses of alcohol a day, diabetes mellites, HTN, hypercholesterolemia, Mini Mental State Examination at baseline examination
(Rajan et al., 2020)	Multinational	145 862	58	35-70	14 years 2005-2019	Short form of the CIDI-SF; cut-off point 4 or more depressive symptoms	F/NF IS and HS	Self-reported through standardised form, household interviews, medical records, death certificates, and other sources(according to ICD-10 I60- I64, I69)	3317	Age, sex, urban/rural residence, educational attainment, use of statins, disabilities former and current smoking and alcohol use, HTN, diabetes, and social isolation index
(Rahman et al., 2013)	EU	36,654	44.4	63	4 years 2006-2009	National patient registers of psychiatrist diagnosis of depression according to ICD-7	IS	National patient register, hospital discharge; death certificates (ICD-10 codes I63-64)	833	Birth year, sex, smoking status, educational level, HTN, diabetes, alcohol intake and BMI

study	Location	N	Men (%)	Age (years)	Length of follow-up (years)	Exposure measure	Outcome	Outcome measure	Cases (n)	Confounder adjustment
(Sico et al., 2018)	USA	106,363	NR	NR	9.2 years	Medical records of CD according to the ICD-9	IS	Medical records of clinical diagnosis according to the ICD-9	NR	Age, sex, race, LDL, HDL, triglyceride, SBP, DBP, diabetes, smoking, BMI, eGFR, haemoglobin, hepatitis C, arterial fibrillation, statin use, cocaine abuse, dependence and alcohol abuse dependence
(Wouts et al., 2008)	EU	2,354*	NA	70.5	10 years 1992-2002	20-item CES-D ≥16, DIS according to DSM-III	F/NF IS and HS	Self-reported confirmed by GP or a cardiac specialist confirming the GP diagnosis of stroke, death certificates (according to the ICD-10 codes I-61, I-63, and I-64.)	NA	Age, sex, Mini-Mental State Examination score, smoking, functional limitations, HTN, diabetes mellitus, and obesity

Abbreviations: AD; antidepressants; BDI, Beck's Depression Inventory; BMI, body mass index; BP, blood pressure; CBVD, cerebrovascular disease; CD, clinical diagnosis; CES-D, Centre for Epidemiological Studies Depression scale; CHD, coronary heart disease; CHF, congestive heart failure; CIDI; Composite International Diagnostic Interview; DBP, diastolic blood pressure, DIS, diagnostic interview schedule; DSM, Diagnostic and Statistical Manual of Mental Disorders; EU, Europe; F, fatal; GADS; Goldberg Anxiety and Depression Scale; GDS, Geriatric Depression Scale; GHQ, General Health Questionnaire; GP, general practitioner; HDL, high density lipoprotein, HTN, hypertension; HS, haemorrhagic stroke; ICD, International Classification of Diseases; IS, ischemic stroke; LDL, low density lipoprotein, MOPSY; MONICA-psychosocial programme; NA; not available; NR, not reported; NF, non-fatal;SBP, systolic blood pressure; TIA, transit ischemic attack; UK, United Kingdom; US, United States. * Participants without cardiac diseases at study baseline.

Recently published studies that were not included in previous meta-analysis are shaded

Table 4-2 Selected characteristics from eligible studies

Study	Type of population	Frequency of measuring depression over study period	Lag period (Yrs)	Assessed dose-response relationship/ type of parameter	Examined independent association between AD and stroke	Loss to follow-up (%)
(Brunner et al., 2014)	Free of CHD and stroke	6 times	Yes (5)	Yes Frequency of being GHQ-30 case	No	0.1
(Daskalopoulou et al., 2016)	Free of CVD	Baseline	No	No	No	NR
(Everson-Rose et al., 2014)	Free of CVD	3 times	No	Yes/ points on CES-D divided into quartiles	Yes	NR
(Gafarov et al., 2013)	Free of CHD, stroke, HTN and diabetes mellitus	Baseline	No	No	No	NR
(Gump et al., 2005)	Free of CHD and stroke but who had above average risk of CHD	Baseline	No	Yes/ points on CES-D divided into quintiles	No	0
(Jee et al., 2019)	Free of CVD	Baseline	Yes (2)	Yes/Number of outpatients visit due to depression	No	0
(Karlsen et al., 2020)	Osteoporois patients free of CVD	Baseline	No	No	No	NR
(Krishnan et al., 2005)	Free of CHD and stroke	Baseline	No	No	No	0
(Li et al., 2012)	Free of stroke and major cardiometabolic diseases	Baseline	No	Yes/Response to AD+ average number of visits within 6 months before stroke incident	Yes	NR
(Li et al., 2019)	Free of CVD	Baseline	No	Yes / points on CES-D divided into quintiles	No	NR
(Majed et al., 2012)	Free of CHD and stroke	Baseline	Yes (5)	No	No	0
(Mathur et al., 2016)	Free of CHD and stroke	Baseline	No	No	Yes	0
(Mejia-Lancheros et al., 2014)	Individuals at high risk but free of CVD	Baseline	No	No	No	NR
(Moise et al., 2016)	Individuals free of CVD	3 times	No	No	No	1.6
(Nabi et al., 2010a)	Individuals free of CHD and Stroke	Baseline	Yes (2)	Yes Symptoms severity / Cut-off points on BDI, 0-9, 10-18 19-29 30-63	Yes	0

Study	Type of population	Frequency of measuring depression over study period	Lag period (Yrs)	Assessed dose-response relationship/ type of parameter	Examined independent association between AD and stroke	Loss to follow-up (%)
(Péquignot et al., 2016)	Individuals free of CHD and stroke	4 times	Yes*	Yes/ Frequency of being CES-D case	No	8
(Rajan et al., 2020)	Free of CVD and cancer	Baseline	No	No	No	2
(Rahman et al., 2013)	Individuals free of CVD	Baseline	No	No	Yes	NR
(Sico et al., 2018)	HIV-ve, free of CVD	Baseline	No	No	No	NR
(Wouts et al., 2008)	Individuals free of CVD	3.4 (mean)	No	No	No	NR

Abbreviations: AD; antidepressants; BDI, Beck's Depression Inventory CES-D, Centre for Epidemiological Studies; CHD, coronary heart diseases; CVD, cardiovascular diseases; GHQ, General Health Questionnaire; HIV, human immunodeficiency virus; HTN, hypertension NR, not reported; Yrs, years, -ve; negative* Outcome reported as a combined endpoint

4.4 Depression and risk of incident stroke

4.4.1 Overall

To generate a consistent analysis, I excluded Krishnan et al. (2005), which reported the risk estimate as an OR. Therefore, the primary analysis included 19 studies. Figure 4-1 demonstrates the results from REM for depression and risk of incident stroke. Of the 19 studies, 11 showed a non-statistically significant association between depression and stroke risk, and nine suggested a statistically significant positive association. At the meta-analysis level, the diamond representing the pooled effect estimates was entirely to the right of the line-of-no-effect, indicating a positive association between depression and stroke incidence. The pooled HR was 1.22 (95% CI, 1.11, 1.33, $p < .0001$) and there was a considerable amount of heterogeneity ($p < .0001$, $I^2 = 67\%$). The observed statistical heterogeneity can be partly explained by the methodological and clinical diversity of Sico et al. (2018) (see Section 4.4.2**).** Three studies (Jee et al., 2019, Péquignot et al., 2016, Sico et al., 2018) carried more than 30% of the overall weight and are thus likely to influence the summary effect.

Finally, a visual inspection of the funnel plot, as shown in Figure 4-2 indicates a slight asymmetry in the distribution of studies at the bottom of the graph. There is a study missing from the bottom left-hand side of the plot (the area of the non-significance), which may indicate the presence of publication bias.

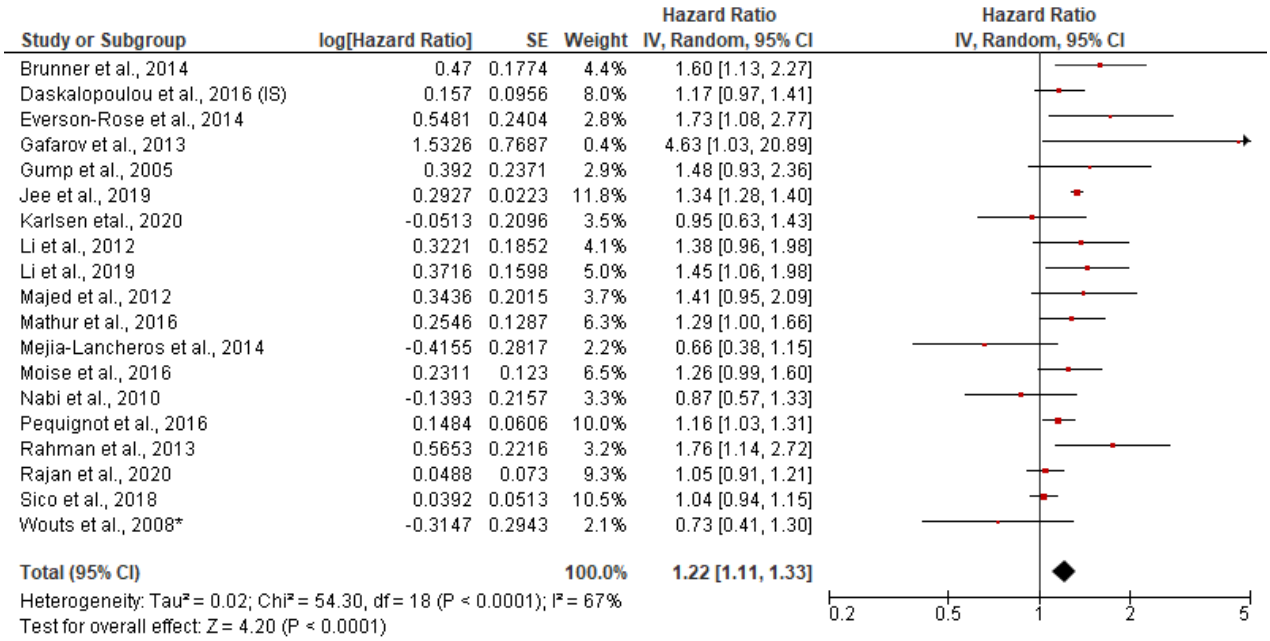

Figure 4-1 Forest plot showing the adjusted HR of stroke incidence for depressed participants compared with non-depressed individuals, overall and in 19 stroke cohorts [RE model].
*, adjusted HR for depressive symptoms; CI, confidence interval; IS, ischemic stroke; IV, inverse variance; SE, standard error

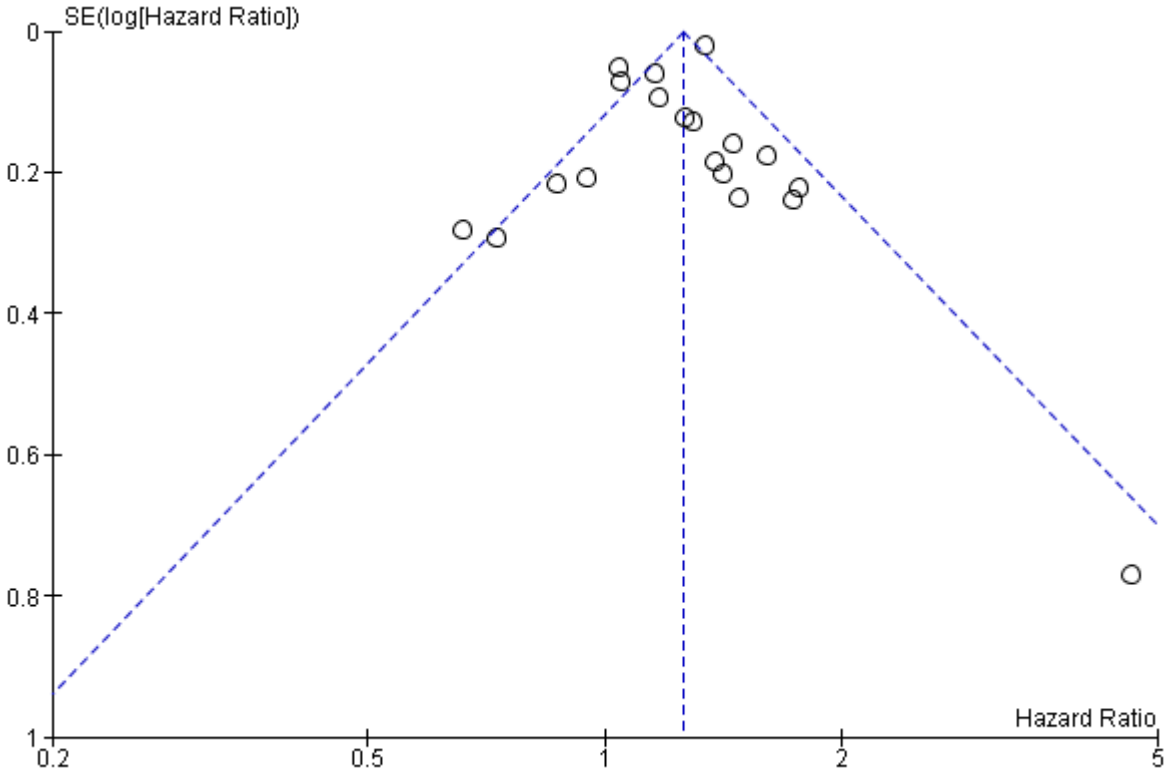

Figure 4-2 Funnel plot from 19 cohorts investigated publication bias
SE, standard error.

4.4.2 **Sensitivity analysis**

Table 4-3 shows the results for the sensitivity analysis according to the prespecified criteria (Section 4.2.2). As shown in Figure 4-3, the exclusion of studies enrolling participants with a high CVD risk (Gump et al., 2005, Mejia-Lancheros et al., 2014) did not significantly affect the pooled risk estimate for stroke (HR = 1.22, 95% CI, 1.12, 1.34). By excluding cohorts that used tools or criteria that were not specifically designed to measure depression (Brunner et al., 2014, Rahman et al., 2013), the magnitude of the estimated effect was slightly attenuated (HR = 1.18, 95% CI, 1.08, 1.30, Figure 4-4). Similarly, there was a slight reduction in the estimated effect (HR = 1.19, 95% CI 1.09, 1.31) after excluding cohorts that were not adjusted for important covariates (Figure 4-5). When restricting the analysis to studies that excluded incident stroke occurring within the first years of follow-up (Figure 4-6), only four studies remained in the analysis and the statistical association between depression and first-ever stroke was more evident (HR = 1.39, 95% CI, 1.11, 1.74). Additionally, I restricted the analysis to include cohorts that treated depression as a time-dependent variable. As shown in Figure 4-7, five studies remained in the analysis, yielding a slight increase in the summary effect compared to the one obtained from the primary analysis with a wider CI (HR = 1.33, 95% CI, 1.10, 1.59, p = 0.003) and a moderate amount of heterogeneity (p of Chi-square test = .25, I^2 = 47%). Notably, the study by Péquignot et al. (2016) greatly influenced the direction of this analysis because it carried about 40% of the total weight. Figure 4-8 demonstrates the results for a meta-analysis of 13 studies that examined the association between depression, CHD and stroke. Compared with the primary analysis, the pooled effect estimate was slightly higher (HR = 1.23, 95% CI, 1.10, 1.37), whereas the heterogeneity between studies was slightly lower (Chi-square test p = 0.06, I^2 = 59%). Additional analyses that examined the influence of a single study on the findings (by omitting a study in each turn) yielded a range of HRs from 1.20 to 1.26 (Table 4-4). None of the studies had a large impact on the estimated risk. However, by excluding Sico et al. (2018) study, the heterogeneity dropped to a moderate estimate, resulting in an I^2 of 56% and a chi-square p-value of 0.002. Likewise, excluding the study conducted by Jee et al. (2019) also reduced the between-study heterogeneity to a similar estimate (I^2 = 50%, *Chi-square* p = 0.008).

Table 4-3 Depression and risk of stroke: Sensitivity analysis summary

Sensitivity analysis		K	HR (95%CI)	*P*-value for heterogeneity	I^2
Overall effect	**REM**	**19**	**1.22 (1.11, 1.33)**	**<0.000**	**67%**
Excluding studies enrolling participants at high risk of CVD	(Gump et al., 2005, Mejia-Lancheros et al., 2014)	17	1.22 (1.12, 1.34)	0.000	67%
Excluding studies used unspecified diagnosis of depression	(Rahman et al., 2013, Brunner et al., 2014)	17	1.18 (1.08, 1.30)	0.000	68%
Excluding studies not controlling for important covariates	(Brunner et al., 2014, Gafarov et al., 2013)	17	1.19 (1.09, 1.31)	0.0007	70%
Studies excluding events occurred with 1st years	(Brunner et al., 2014, Jee et al., 2019, Majed et al., 2012, Rahman et al., 2013)	4	1.39 (1.11, 1.74)	0.005	58%
Studies reported risk of time-varying depression	(Everson-Rose et al., 2014, Moise et al., 2016, Péquignot et al., 2016, Wouts et al., 2008)	5	1.33 (1.10, 1.59)	0.02	42%
Studies examined CHD and stroke outcomes simultaneously within the same population	(Brunner et al., 2014, Daskalopoulou et al., 2016, Gafarov et al., 2013, Jee et al., 2019, Karlsen et al., 2020, Majed et al., 2012, Mathur et al., 2016, Mejia-Lancheros et al., 2014, Moise et al., 2016, Nabi et al., 2010a, Péquignot et al., 2016, Rahman et al., 2013, Rajan et al., 2020)	13	1.23 (1.10,1.37)	0.003	59%

Abbreviations: CI, confidence interval; CHD; coronary heart diseases; CVD; cardiovascular diseases; HR, hazard ratio; I^2, I-square test; K; number of studies; MDD, major depressive disorders; REM, random-effect model.

Table 4-4 Depression and risk of stroke: Sensitivity analysis excluding studies in turn (leave-one-out approach)

Study	HR (95%CI)	*P*-value for heterogeneity	I^2
Overall effect (REM)	1.22 (1.11, 1.33)	<0.000	67%
(Brunner et al., 2014)	1.20 (1.09,1.32)	0.000	68%
(Daskalopoulou et al., 2016)	1.22 (1.11, 1.34)	0.000	68%
(Everson-Rose et al., 2014)	1.20 (1.10, 1.32)	0.000	68%
(Gafarov et al., 2013)	1.21 (1.11, 1.32)	0.000	67%
(Gump et al., 2005)	1.21 (1.10, 1.33)	0.000	68%
(Jee et al., 2019)	1.20 (1.09, 1.31)	0.008	50%
(Karlsen et al., 2020)	1.23 (1.12, 1.34)	0.000	68%
(Li et al., 2012)	1.21 (1.10, 1.33)	0.0000	69%
(Li et al., 2019)	1.20 (1.10, 1.32)	0.000	68%
(Majed et al., 2012)	1.21 (1.10, 1.33)	0.000	69%
(Mathur et al., 2016)	1.21 (1.10, 1.33)	0.000	69%
(Mejia-Lancheros et al., 2014)	1.23 (1.13, 1.34)	0.000	65%
(Moise et al., 2016)	1.21 (1.10, 1.34)	0.000	69%
(Nabi et al., 2010a)	1.23 (1.12, 1.35)	0.000	67%
(Péquignot et al., 2016)	1.22 (1.11, 1.35)	0.000	68%
(Rahman et al., 2013)	1.20 (1.10, 1.32)	0.000	67%
(Rajan et al., 2020)	1.23 (1.12, 1.36)	0.000	64%
(Sico et al., 2018)	1.24 (1.13, 1.35)	0.002	56%
(Wouts et al., 2008)	1.23 (1.12, 1.34)	0.000	67%

HR, hazard ratio; REM, random effect model

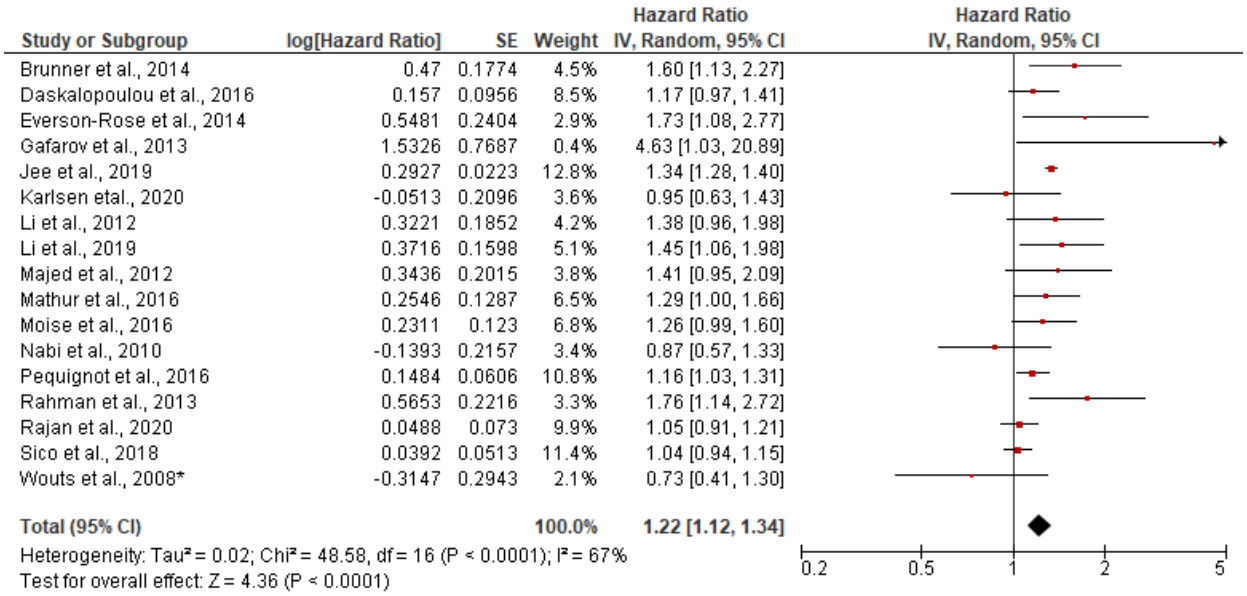

Figure 4-3 Forest plot showing the adjusted HR of stroke for depressed participants compared with non-depressed individuals [Sensitivity analysis: Excluding studies enrolled participants at high risk of developing CVD]
CI, confidence interval; IV, inverse variance; SE, standard erorr

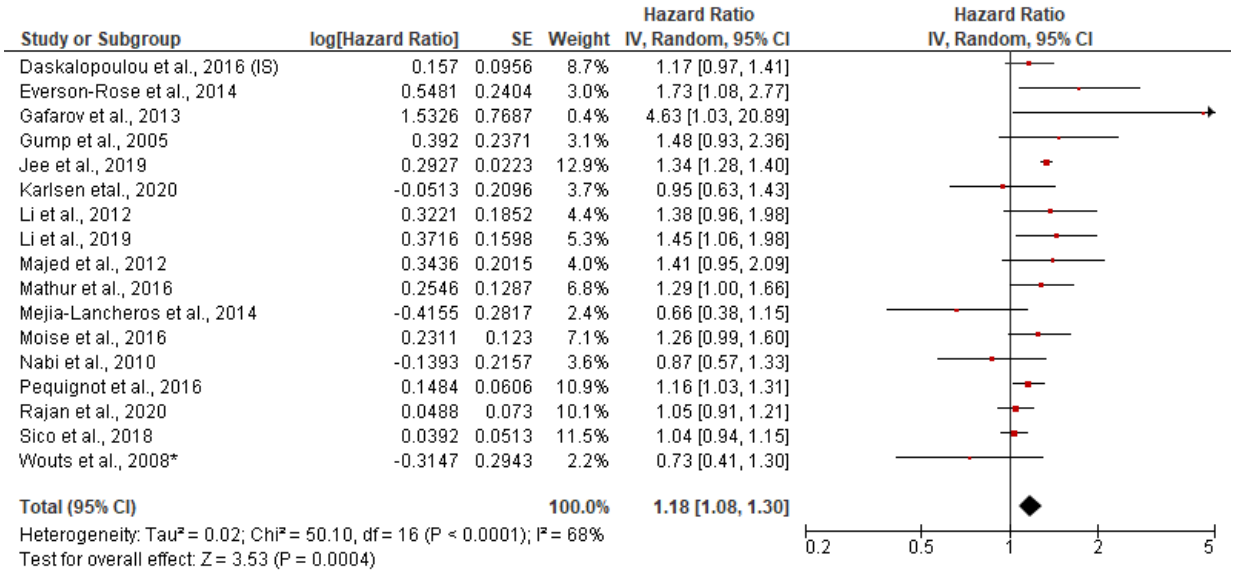

Figure 4-4 Forest plot showing the adjusted HR of stroke for depressed participants compared with non-depressed individuals [Sensitivity analysis: Excluding studies used unspecified diagnostic or screening tools to identify cases of depression]
CI, confidence interval; IV, inverse variance; SE, standard erorr

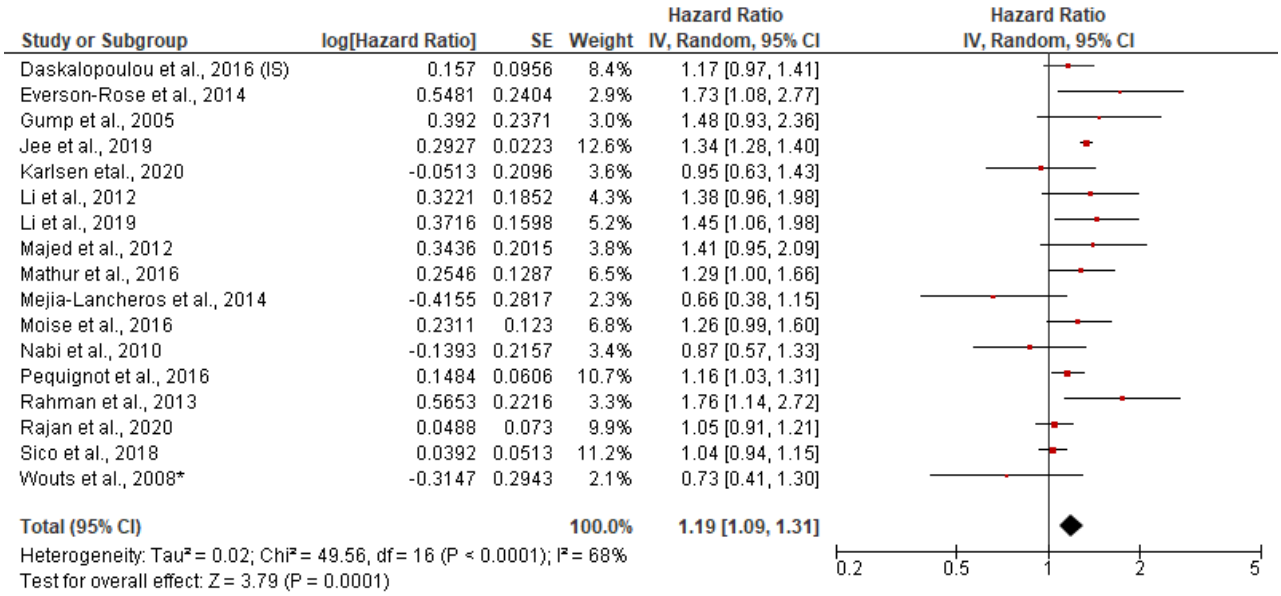

Figure 4-5 Forest plot showing the adjusted HR of stroke for depressed individuals compared with non-depressed individuals [Sensitivity analysis: Excluding studies not adequately adjusted for potential confounders]
CI, confidence interval; IV, inverse variance; SE, standard erorr

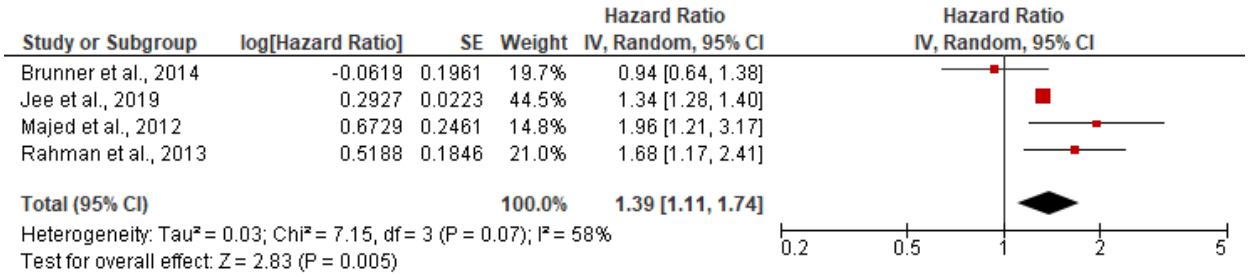

Figure 4-6 Forest plot showing the adjusted HR of stroke for depressed participants compared with non-depressed individuals [Sensitivity analysis: studies excluded stroke incident occurred within the first years].
CI, confidence interval; IV, inverse variance; SE, standard error

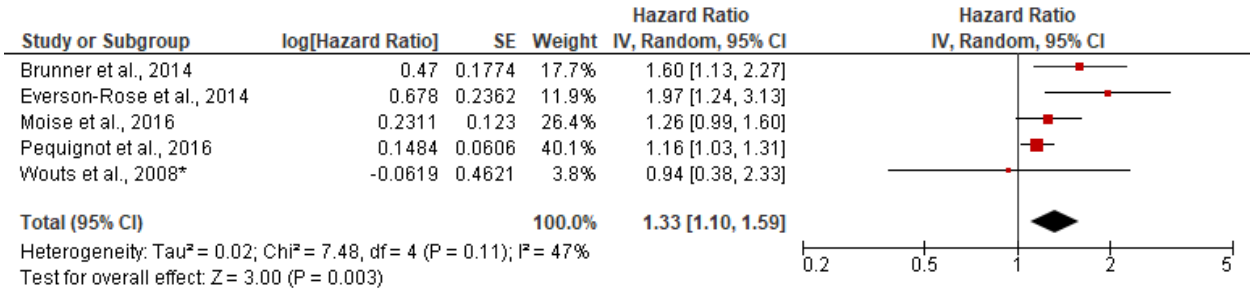

Figure 4-7 Forest plot showing the adjusted HR of stroke for depressed individuals compared with non-depressed individuals [Sensitivity analysis: studies assessed depression as a time-dependent exposure]

*, adjusted HR for depressive symptoms; CI, confidence interval; IV, inverse variance; SE, standard error.

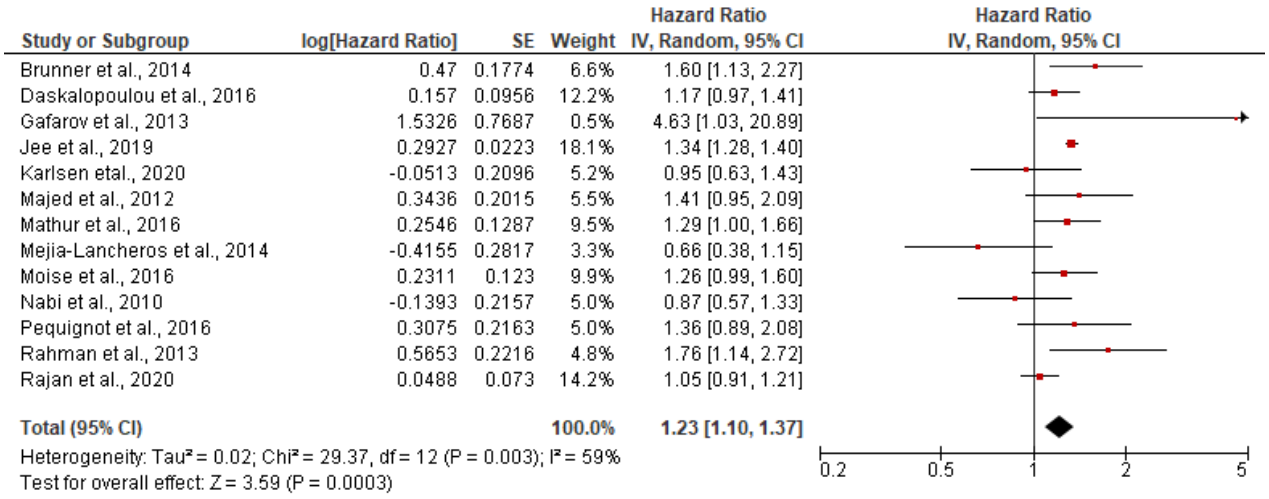

Figure 4-8 Forest plot showing the adjusted HR of stroke for depressed participants compared with non-depressed individuals [Sensitivity analysis: Including cohorts that examined risk of developing stroke and CHD simultaneously as their primary outcomes and calculated the HRs for each outcome separately]
CI, confidence interval; IV, inverse variance; SE, standard error

4.4.3 Depression and risk of incident stroke: Subgroup analysis

Table 4-5 summarises the results for the subgroup analyses for depression and stroke risk. Altogether, seven subgroups were categorised by type of depression assessment, study follow-up duration, mean age groups, stroke subtype, CVD condition at baseline, sample size and geographical location of the study. The results from the primary overall analysis are included for reference.

4.4.3.1 By type of depression assessment

Eleven studies reported data for depression assessment using SRS, enrolling 108,069 participants. Data synthesis of these studies resulted in an HR of 1.28, a 95% CI between 1.12 and 1.46 and a *p*-value of 0.004 **(**Figure 4-9). None of the studies principally influenced this analysis. Heterogeneity between studies was markedly reduced, evident by the I^2 statistic, which was observed at 35% and a chi-square test resulted in a *p*-value of 0.12, indicating no statistically significant heterogeneity between the studies. Data for depression assessment using clinical diagnosis were available from seven studies, enrolling 794,919 participants (Figure 4-9). The combined HR from this analysis was 1.13, with a 95% CI between 0.98 and 1.31 ($p = 0.10$). The direction of this finding was greatly driven by Sico et al. (2018) and Rajan et al. (2020) because their studies carried more than 50% of the total weight. There was a substantial amount of heterogeneity between studies, as indicated by the chi-square test ($p = .04$) and the I^2 test, which was observed at 54%. Data for depression assessment relying on valid prescriptions of antidepressants and/or combined with a clinical diagnosis were available for three studies with 2,455,369 participants. Pooling the effect estimates yielded an HR of 1.34 (95% CI, 1.16-1.55) with a *p*-value of < .0001 (Figure 4-9). The I^2 test for heterogeneity was observed at 56%, and the chi-square test yielded a *p*-value of 0.1. Three studies investigated the relationship between antidepressants and stroke with 584,888 participants. The summary effect estimate was an HR of 1.11, with a 95% CI between 0.96 and 1.28 and a *p*-value of .17 (Figure 4-9). Mathur et al. (2016) and Rahman et al. (2013) studies both had a large impact on the direction of this analysis (total weights of 48% and 46.9%, respectively). Testing for heterogeneity resulted in a chi-square *p*-value of 0.37 and an I^2 statistic of 1%, indicating no significant difference between the studies. The test for subgroup

differences indicated that no statistically significant subgroup effect existed (p = .18).

4.4.3.2 **By duration of follow-up**

Studies with a follow-up duration of 10 years or longer were available from 12 cohorts (3,135,614 participants). Combined effect estimates resulted in an HR of 1.24 with a 95% CI between 1.12 and 1.37 and a p-value of < .0001 (Figure 4-10). Assessment of heterogeneity revealed substantial differences between studies confirmed by I^2 statistics test, which observed at 59% and chi-square test p-value of .01. Meanwhile, data for studies with a follow-up of less than 10 years were available from 1,80,116 participants enrolled in seven cohorts. The pooled HR was 1.18 with a 95% CI between 0.98 and 1.41 and a p-value of .08 (Figure 4-10). Moderate to high heterogeneity was detected with an I^2 statistics test result of 62% and a p-value of .01 for the chi-square test. No statistically significant differences exist between the two groups (p = 0.63).

4.4.3.3 **By mean age groups**

Data for studies with a younger mean age (<65 years) were available from 3,227,725 patients enrolled in 14 cohorts. Figure 4-11 shows the estimated HR (1.30, 95% CI, 1.18-1.42; p < .00001). A moderate heterogeneity was found with an I^2 = 44% and a chi-square test p-value of 0.04. However, for studies of patients with a mean age of 65 years or older, data were available from four studies comprising 18,805 participants. These studies yielded a non-significant association between depression and incident stroke. The pooled HR, as shown in Figure 4-11 was 0.92 (95% CI, 0.67-1.27, p =0.63). Moderate heterogeneity was evident by an I^2 of 43% and a chi-square test p-value of 0.16. The test for subgroup differences was borderline statistically significant (p =0.05).

4.4.3.4 **By stroke subtypes**

Fifteen studies with 791,161 participants reported a combined endpoint for fatal/non-fatal stroke. Analysing these studies produced a pooled HR of 1.23 (95% CI, 1.08-1.39, p = .002 (Figure 4-12). Assessment of heterogeneity by the chi-square test resulted in a p-value of 0.02. I^2 statistics test results showed 47%, detecting moderate to substantial heterogeneity. Data for ischemic stroke were

available from six cohorts enrolling 2,544,528 patients. The combined estimate of HR was 1.16 with a 95% CI between 1.02 and 1.31, p = 0.02 (Figure 4-12). Heterogeneity between studies was substantial (I^2 = 70%, *chi-square* test p = 0.006). Two studies with 2,418,715 participants provided data for haemorrhagic stroke and pooling effect estimates from these studies yielded an HR of 1.09 (95% CI, 0.98, 1.22) and a p-value of 0.11 (Figure 4-12). A heterogeneity assessment showed a chi-square p-value of 0.87 and I^2 statistics of 0%, indicating a trivial difference between studies. Visually, the influence of Jee et al. (2019) study in the analysis was apparent, as it was represented by the largest box corresponding to its weight (86%). No statistically significant subgroup effect (p = 0.41).

4.4.3.5 **By CVD status at baseline**

Nine studies enrolling 594,329 participants defined their population as free of both CHD and stroke. As shown in Figure 4-13, pooling the effect estimate from the nine studies resulted in an HR of 1.29 (95% CI, 1.09, 1.53, p = .003). The results from all cohorts included in this analysis are relatively homogenous (p = .15, I^2 = 33%). However, 10 studies with 2,725,020 extended this definition to exclude patients with CVD conditions. The combined effect estimates resulted in a lower HR compared to the above group (HR = 1.19, 95% CI, 1.06, 1.34, p = .004). There was, however, considerable statistical heterogeneity between these studies (p < .00001, I^2 = 80%). Test for subgroup differences showed no statistically significant group effect (p = .43).

4.4.3.6 **By sample size**

Figure 4-14 illustrates meta-analyses results stratified based on studies sample size. Eight studies enrolled less than 10,000 of individuals and results showed non statistically significant association between depression and risk of stroke (HR= 1.19 95%CI 0.92,1.54). Pooling results from six studies with total participants between 10,000 and 100,000 yielded a statistically significant association but with a larger magnitude comparing to the primary results (HR= 1.37 95%CI 1.15, 1.62). Finally, a subgroup analysis of five studies with extremely large sample size enrolling more than or equal to 100,000 showed a statistically significant association with a HR of 1.17 and a 95%CI between 1.01 and 1.35 with considerable amount of heterogeneity (I^2= 85%). It should be noted that among the five studies

only Jee et al.'s showed a statistically significant association result with a 95%CI that not included one. It also had the largest weight comparing to other four studies (25%). To ensure that the overall meta-analysis result was not driven by this study I excluded Jee et al., study and the results obtained showed that depression remained statistically significantly associated with incident stroke (HR= 1.08, 95%CI 1.00, 1.17; *p*= 0.04).Despite the discrepancy in the results in terms of the magnitude, results from large studies were consistently in the same direction showing positive association.

4.4.3.7 **By study location**

Figure 4-15 shows data stratified according to the study location. Ten cohorts were conducted in Europe, enrolling 2,559,375 participants. The combined estimate of HR was 1.21 (95% CI, 1.02-1.44, p = .03). Substantial heterogeneity was observed as indicated by an I^2 statistic test (51%) and a chi-square test (p = .03). Five studies were conducted in the United States with 115,325 patients. As shown in Figure 4-15 a meta-analysis of these studies resulted in an HR of 1.19 (95% CI, 0.99-1.42, p = .06) with moderate heterogeneity (I^2 = 50%, p = .06). This result was mainly influenced by the Sico et al. (2018) study, which accounted for 40% of the total weight. Data for studies in Asia were available from 498,787 participants enrolled in three studies. The effect of depression in this subgroup was more pronounced compared to the European and American populations (HR = 1.34, 95% CI, 1.29, 1.40, p < .000). The result was mostly driven by Jee et al. (2019) study, which carried the most weight (96.7%). The results of the subgroup analysis suggested that no statistically significant subgroup effect existed (p = .25).

Table 4-5 Depression and risk of stroke: Subgroup analysis summary

Subgroup analysis		K	N of participants	HR (95%CI)	*P*-value for heterogeneity	I^2	Between-group *P*-value
Overall effect	**REM**	**19**	**3,314,334**	**1.22 (1.11, 1.33)**	**0.000**	**67%**	
Type of depression assessment	SRS	11	108,069	1.28 (1.12, 1.46)	0.12	35%	0.18
	Clinical diagnosis	7	794,919	1.13 (0.98,1.31)	0.04	54%	
	Combined clinical diagnosis and AD use	3	2,455,369	1.34 (1.16,1.55)	0.10	56%	
	AD	3	584,888	1.11 (0.96,1.28)	0.37	1%	
Duration of follow-up	< 10 years	7	1,80,116	1.18 (0.98, 1.41)	0.01	62%	0.63
	≥ 10 years	12	3,135,614	1.24 (1.12, 1.37)	0.004	59%	
Mean age	< 65 years	14	3,227,725	1.30 (1.18,1.42)	0.04	44%	**0.05**
	≥ 65 years	4	18,805	0.92 (0.67,1.27)	0.16	43%	
Stroke subtypes	Fatal/non-fatal stroke	15	791,161	1.23 (1.08, 1.39)	0.002	47%	0.41
	IS	6	2,544,538	1.16 (1.02, 1.31)	0.006	70%	
	HS	2	2,418,715	1.09 (0.98, 1.22)	0.87	0%	
CVD status at baseline	Free of CHD and stroke	9	594, 329	1.29 (1.09, 1.53)	0.15	33%	0.43
	Free of CVD	10	2,725,020	1.19 (1.06, 1.34)	0.000	80%	
Sample size	≥ 100,000	5	3162348	1.17 (1.01,1.35)	0.0001	86%	0.36
	≥ 10,000 and <100,000	6	116271	1.37 (1.15, 1.62)	0.000	30%	0.21
	< 10,000	8	40,730	1.19 (0.92, 1.54)	0.03	55%	
Study location	EU	10	2,559,375	1.21 (1.02, 1.44)	0.03	51%	0.51
	US	5	115,325	1.19 (0.99, 1.42)	0.09	50%	
	Asia	3	498,787	1.34 (1.29, 1.40)	0.88	0%	

Abbreviations: AD, antidepressants; CI, confidence interval; CHD, coronary heart disease; CVD, cardiovascular disease; EU; Europe; HR, hazard ratio; HS; Haemorrhagic stroke; K; number of studies; IS, ischemic stroke; SRS, self-reported scale; N; number; REM, random effect model; US, United states.

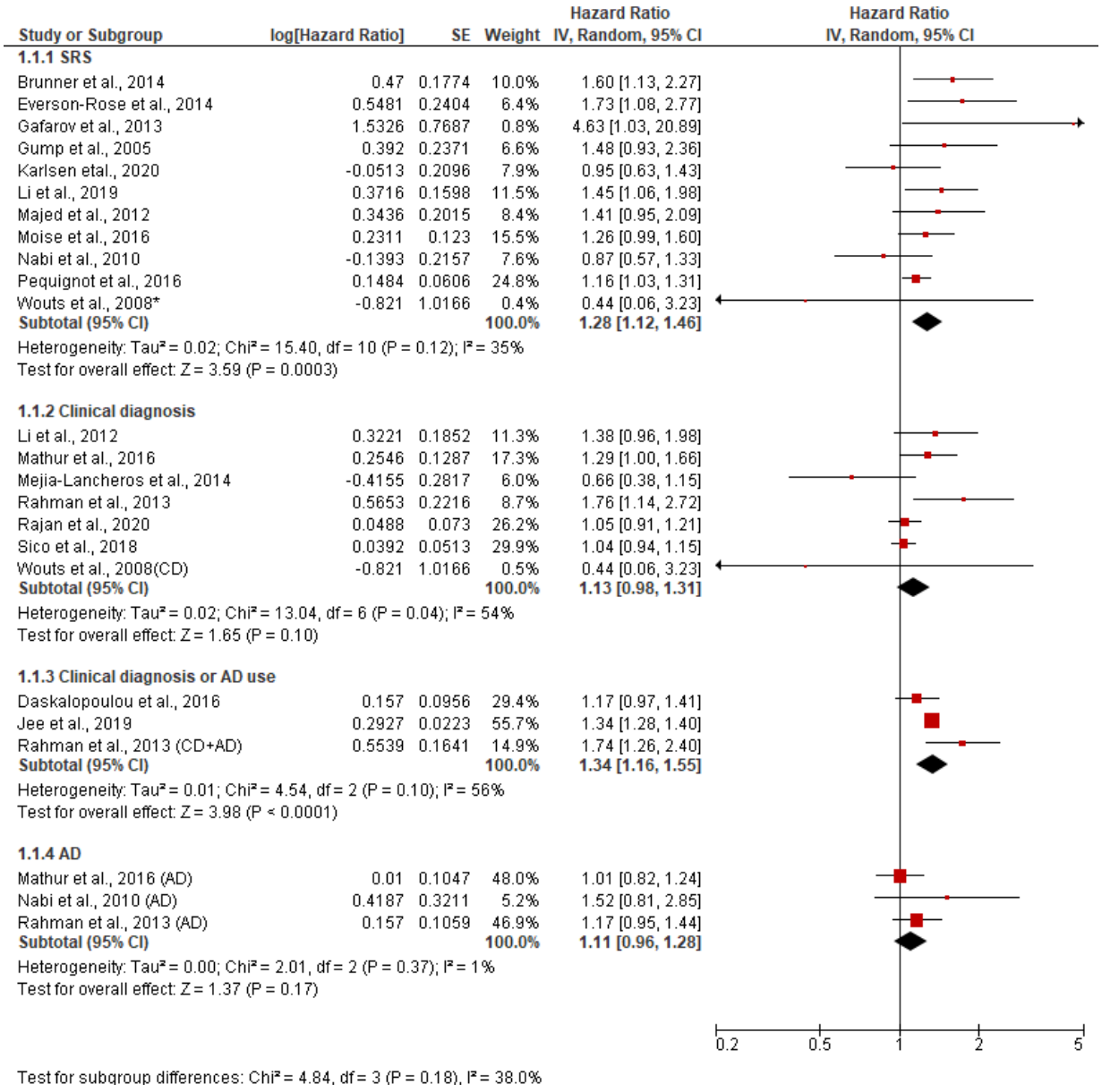

Figure 4-9 Forest plot showing the adjusted HR of stroke incidence for depressed individuals compared with non-depressed individuals by type of depression assessment
AD, antidepressants; CD, clinical depression; CI, confidence interval; IV, inverse variance; SE, standard error; SRS, self-reported scale

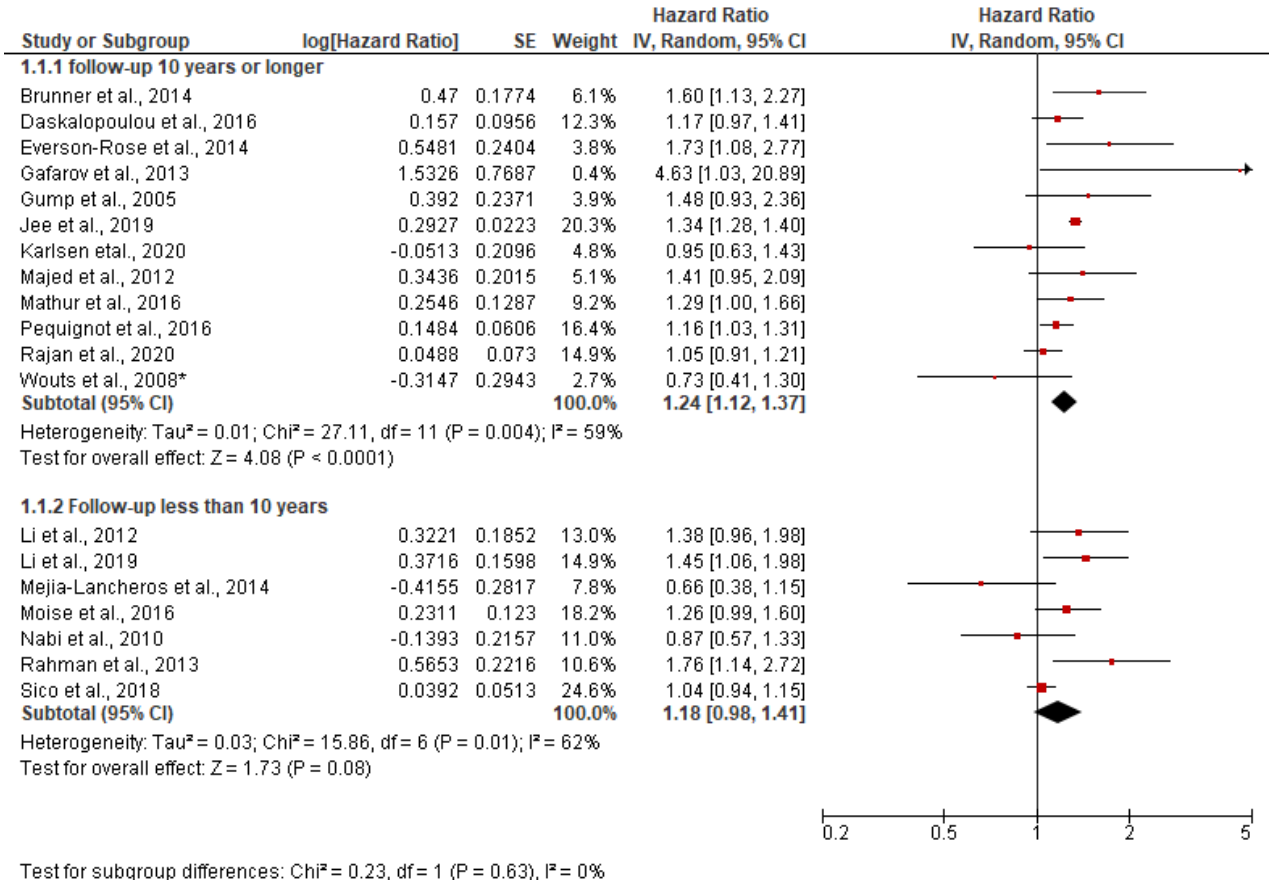

Figure 4-10 Forest plot showing the adjusted HR of stroke incidence for depressed individuals compared with non-depressed individuals by duration of follow-up
CI, confidence interval; IV, inverse variance; SE, standard error

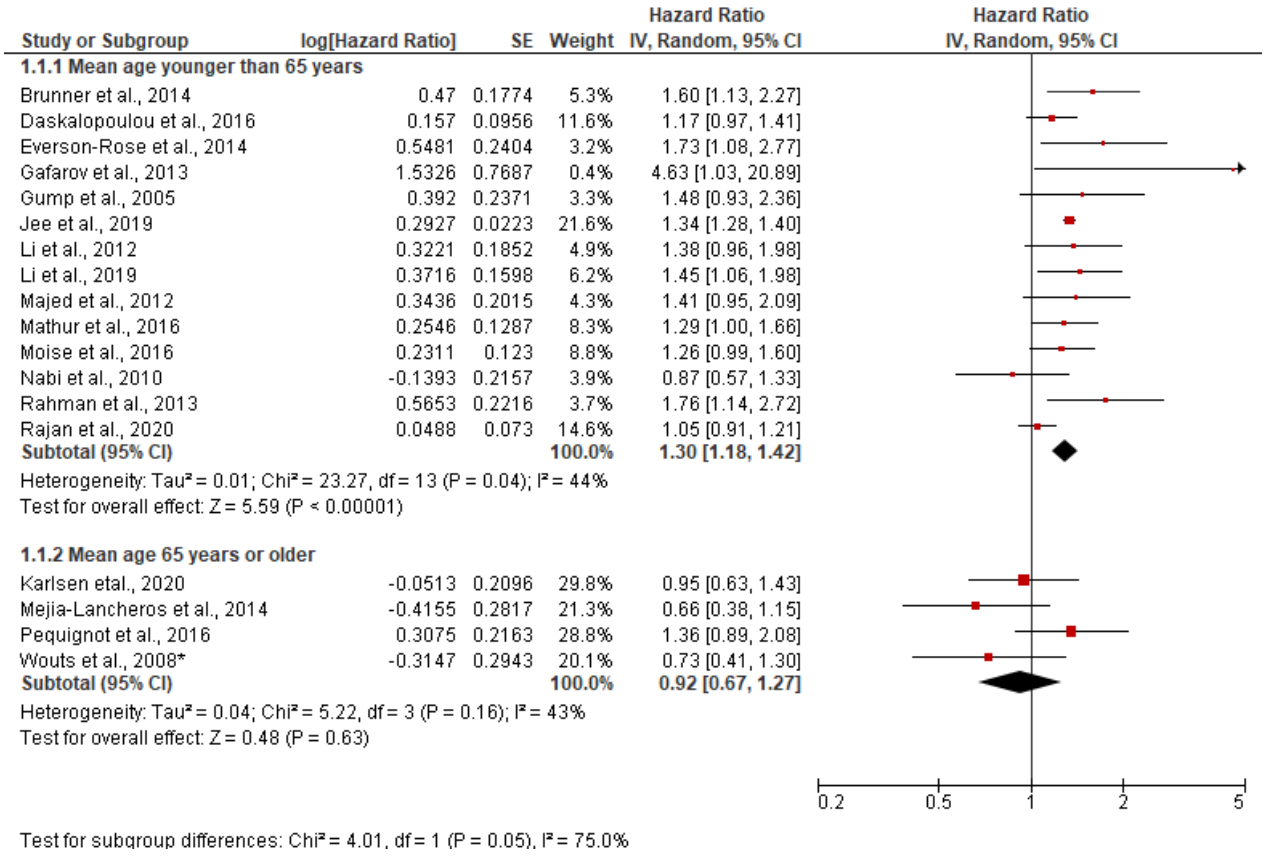

Figure 4-11 Forest plot showing the adjusted HR of stroke incidence for depressed individuals compared with non-depressed individuals by study population's mean age
CI, confidence interval; IV, inverse variance; SE, standard error

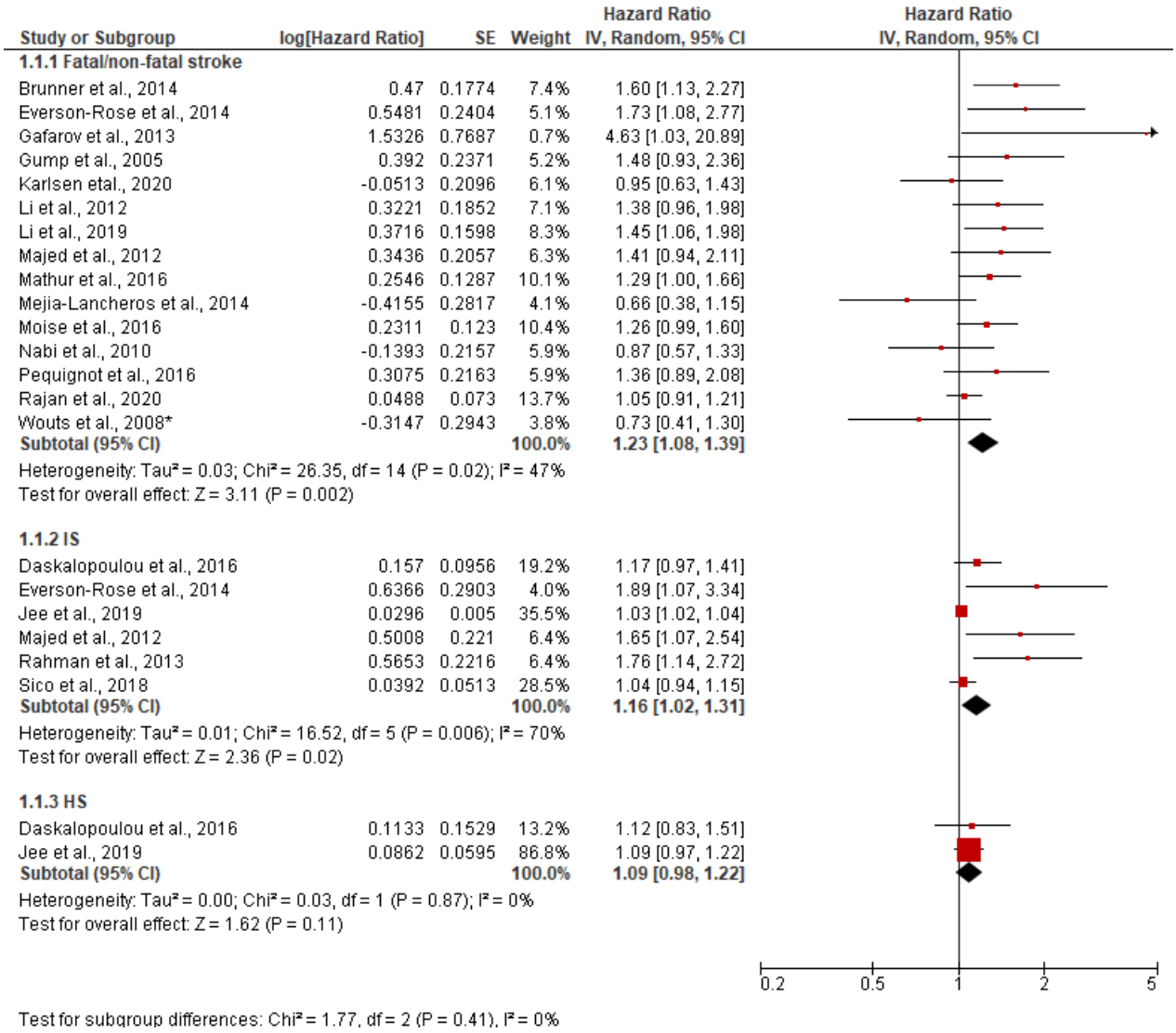

Figure 4-12 Forest plot showing the adjusted HR of stroke incidence for depressed individuals compared with non-depressed individuals by stroke subtypes
CI, confidence interval; HS; haemorrhagic stroke; IS, ischemic stroke; IV, inverse variance SE, standard error

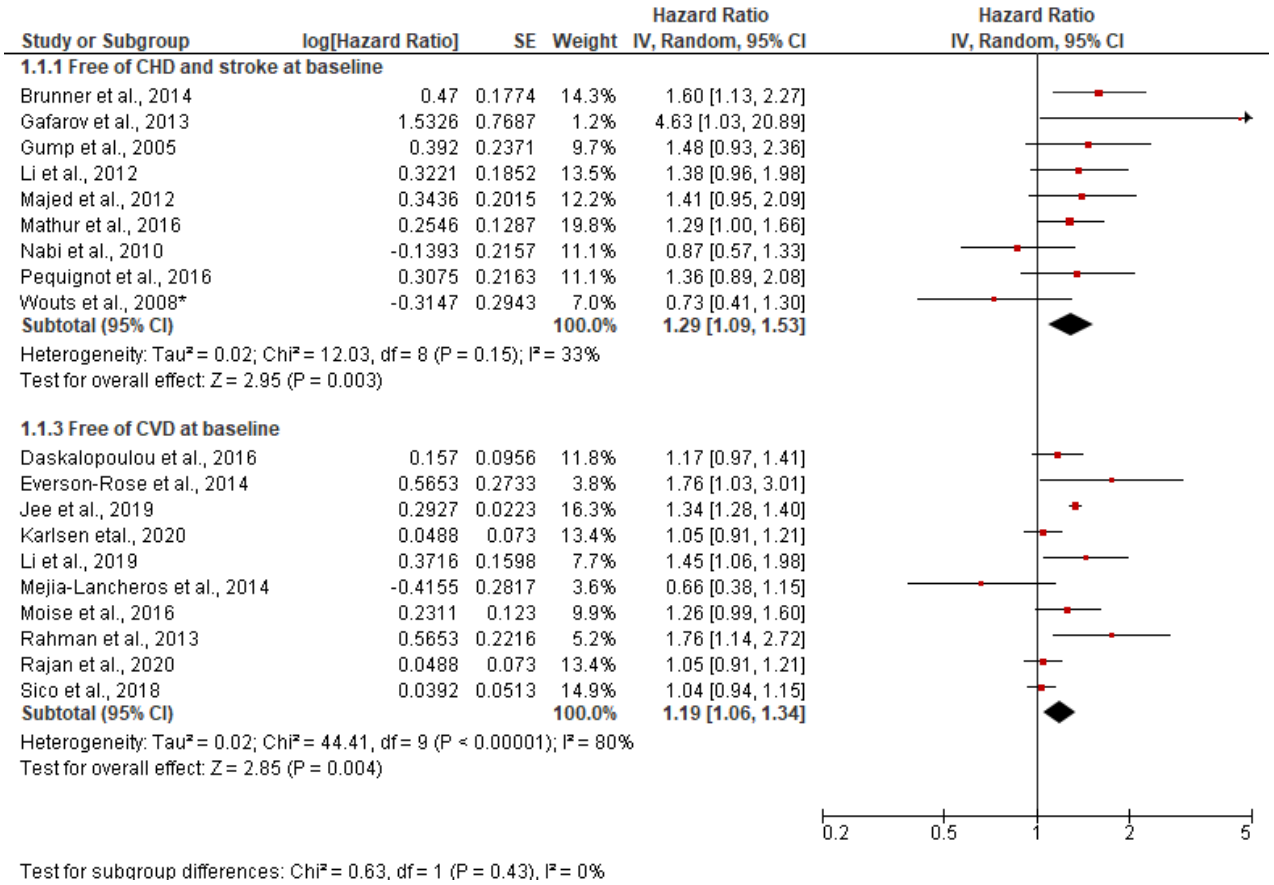

Figure 4-13 Forest plot showing the adjusted HR of stroke incidence for depressed individuals compared with non-depressed individuals by CVD status

CHD; coronary heart diseases; CI, confidence interval; CVD, cardiovascular diseases; IV, inverse variance; SE, standard error

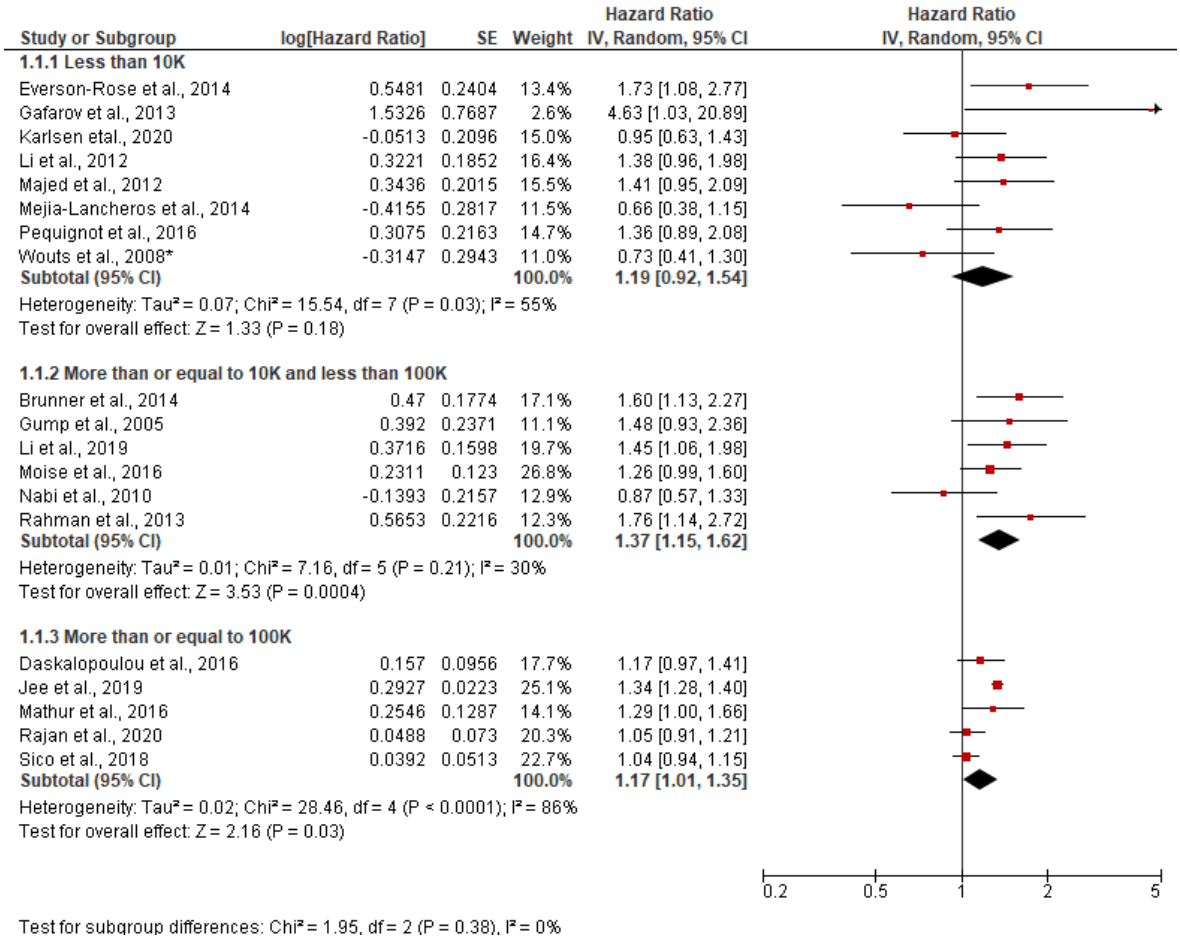

Figure 4-14 Forest plot showing the adjusted HR of stroke incidence for depressed participants compared with non-depressed individuals by study sample size
CI, confidence interval; IV, inverse variance; SE, standard error

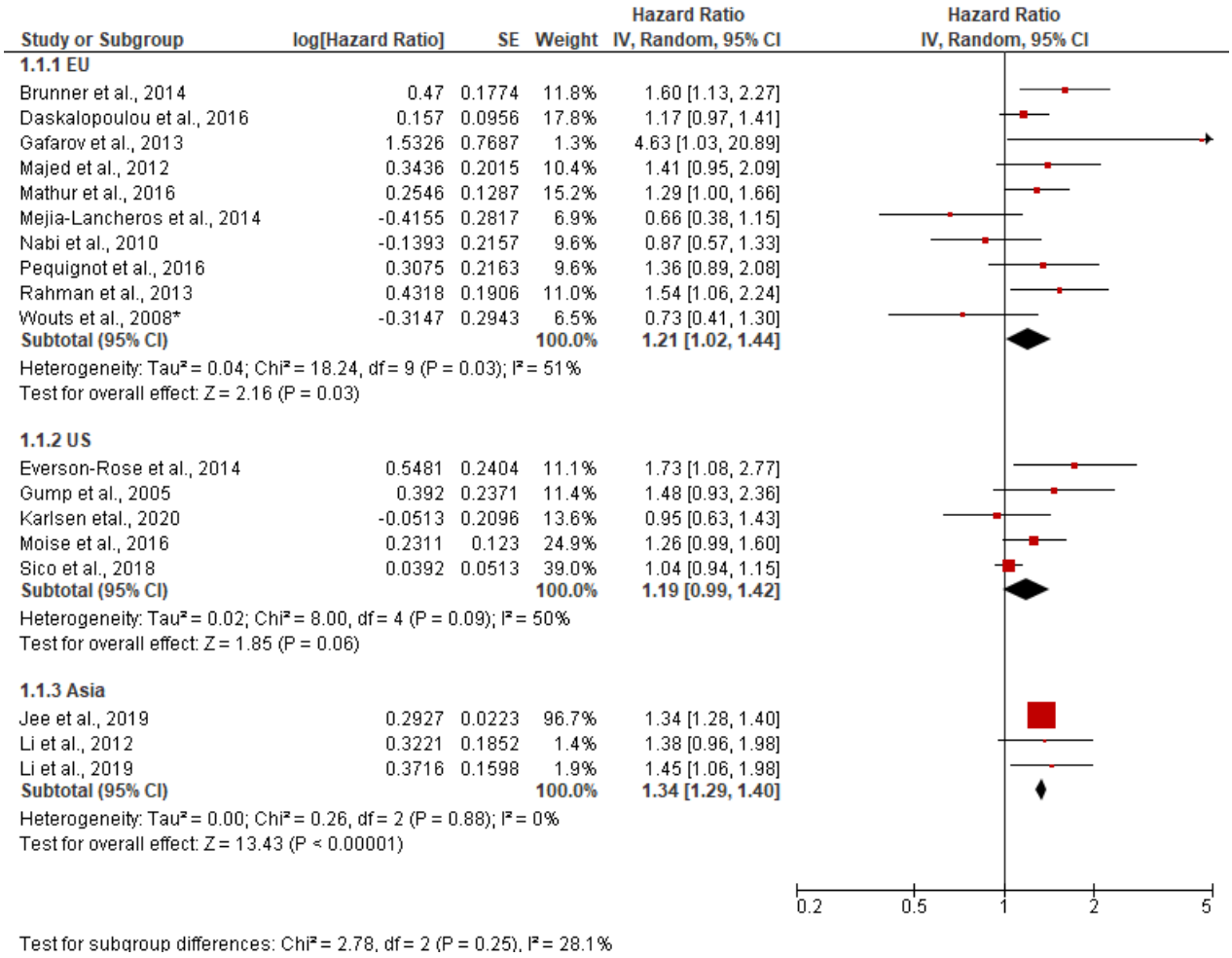

Figure 4-15 Forest plot showing the adjusted HR of stroke incidence for depressed participants compared with non-depressed individuals by study geographical location
CI, confidence interval; IV, inverse variance; SE, standard error

4.5 Discussion

This study investigates the association between depression and first-ever stroke in patients free of stroke and CHD at baseline. The findings from 19 prospective cohort studies suggested that depression was associated with a 22% increased risk of stroke. This was demonstrated in the REM (HR 1.22, 95% CI, 1.11-1.33) with evidence of a substantial heterogeneity between studies (I^2 = 67%, p < .0001). Overall, the main findings did not significantly change in most of the subgroup and sensitivity analyses. The association between depression and stroke derived from studies that measured CHD and stroke outcomes simultaneously within the same population yielded a very close estimate effect (HR = 1.23, 95% CI, 1.10, 1.37, I^2 = 59%). Nevertheless, in some analysis there were studies shifted the trend towards non-significance. The following sections discuss the results obtained from these analyses.

4.5.1 Dose response relationship

I investigated the dose-response relationship between depression and stroke, which is often a function of both the level and duration of exposure. However, few studies in this review investigated a possible dose-response relationship. If depression is considered a traditional risk factor for stroke, then we should expect an incremental increase in the risk of future stroke as depression severity/chronicity increases. This review tested six studies for a dose-response effect between depression and stroke (Brunner et al., 2014, Everson-Rose et al., 2014, Gump et al., 2005, Jee et al., 2019, Li et al., 2012, Péquignot et al., 2016), which adopted various methodological differences, including different measures of depression, different risk indexes and different ranges of scores within the same scale used to generate multiple categories of increasing severity. Therefore, since there was no standardised approach among the studies, it was impossible to pool the data results. Thus, in the following section, I only describe and discuss their results narratively. To measure the severity of depressive symptoms, Gump et al. (2005) and Everson-Rose et al. (2014) used the 20-item CES-D (score range 0-60) in their studies to measure depressive symptoms and examine the dose-response association related to symptom severity. They divided the CES-D score into five groups, but each used distinct cut-off points. Gump et al. (2005) used 0-1 and 13-60 scores to represent the lowest and highest risk groups, respectively, while

Everson-Rose et al. (2014) classified the lowest risk group as having a 0-2 score and the highest risk group as having a score of more than or equal to 16. Gump et al. (2005) presented a significant linear association between depressive symptoms quartiles and risk of stroke (*p*-value for trend = .002), though after modelling depression as a binary variable (<16 and ≥16), the statistically significant association between depression and stroke did not survive. Correspondingly, Everson-Rose et al. (2014) found a gradient of increasing stroke risk as the severity of depressive symptoms increases (*p*-value for trend = .03). Notably, this approach addresses dose-response associations of stroke with depressive symptoms but not clinical depression. Further, the trend of association in both studies was presented only for minor symptoms (i.e. a score of <16 indicates nil or mild symptoms) and did not present how the dose-response relationship looked beyond that point to evaluate the stability of this relation over higher levels of depressive symptoms. In contrast to these two studies, Nabi et al. (2010a) measured depressive symptoms with the BDI tool and used standardised cut-off scores to incorporate different levels of severity; however, no evidence was found of a dose-response association between depression and stroke. Li et al. (2019) used the 10-item CES-D scale (score range of 0-30) to quantify depressive symptoms. The scores were then split into quintiles, where the first quintile (score of 0-2) represented the lowest risk group and the fifth quintile (score of 15-30) represented the highest risk group. The results showed a linear and positive association between the CES-D total score and risk of incident stroke, although a statistical significance association with stroke risk was only observed for the highest quintile. Li et al. (2012) applied two different approaches to explore a dose-response relationship in terms of symptoms severity. First, they categorised depressed patients based on their baseline response to antidepressant medication into three groups: easy to treat, intermediate to treat and difficult to treat. Their results showed no statistically significant differences between the three groups in terms of stroke rate. However, antidepressant refractoriness may not be an ideal marker to evaluate depression severity, as this may reflect individual differences. The second approach was to retrospectively measure the levels of depressive symptoms before the stroke index date using the average number of psychiatric visits as an indicator. They found that the average number of psychiatric visits within the last six months before stroke onset was significantly higher among stroke patients compared to the control depressed patients. Although this method

has the advantage of avoiding recall bias, as they had relied on hospital records to extract information rather than patient interviews, it measured depressive symptoms' intensity over a short period (six months prior to the event), which might also originate from subclinical CVD; thus, reverse causality cannot be ruled out. Regarding depression chronicity, Jee et al. (2019) used the number of outpatients visits, up to 10 visits, due to MDD as a proxy for severity of depression and showed a gender differences response. The results showed that the risk of stroke incidence was more profound with 3-4 visits; however, this risk was no longer statistically significant after 10 or more visits. With regards to women, they showed that the risk of stroke incidents increases with the increasing number of outpatient visits. On the contrary, Brunner et al. (2014) measured depressive symptoms seven times over the follow-up period, and using the frequency of exhibiting clinically related depressive symptoms, they provided no evidence for a dose-response relationship. Péquignot et al. (2016) measured depressive symptoms at four study visits and found that the risk of first-ever stroke was evident with both transient and cumulative exposure to depressive symptoms. Previous meta-analyses have not examined whether depression follows a dose-response relationship to stroke risk. On balance, the results of this analysis are inconclusive in relation to a dose-response relationship due to the relatively small number of studies included and substantial methodological heterogeneity. However, based on what is known to date, I can conclude that even one episode of mild depression cannot be considered safe, as the probability of having a first-ever stroke might be the same with mild-to-moderate depression as it is with severe depression and with one episode as it is with multiple episodes of depression.

4.5.2 **Depression as a time-varying exposure**

The nature of depression is complex. Symptoms can improve and deteriorate over time, and patients can switch between categories (Gilchrist and Gunn, 2007). However, this fluctuating course can be missed in studies with short follow-up duration and in the case of a lack of repeated measures over the study period. This variation was noticed in my subgroup analysis based on the follow-up duration as I found that depression is associated with a significant increased risk of developing stroke in the group of more than or equal to 10 years of follow-up but

not in the group with less than 10 years follow-up, though the difference was not statistically significant (p = .63). This finding may be partially explained by the number of stroke events, as a longer follow-up will inevitably lead to more events. More importantly, not all studies accounted for time-varying risk factors. As mentioned, depression as a cluster of symptoms as well as other risk factors confounding the associations between depression and stroke (e.g. health-related variables) are likely to change throughout a long study duration. Therefore, in this subgroup, the significant observation over a long follow-up period may not be due to an actual 'strengthening' of the association but may be due to the decreased accuracy of baseline data. One possible solution is to analyse depression as a time-varying variable because it is more likely to afford robust findings compared to baseline depression. As a secondary aim, I sought to evaluate the stability of the association between depression and stroke over time. I performed a sensitivity analysis incorporating fivestudies measured depressive symptoms at least three times over the follow-up period interval and modelled depression as a time-varying variable in Cox's proportional hazard model. I found that depressive symptoms are associated with a 27% (HR = 1.27, 95% CI, 1.05, 1.53; I^2 = 42%) increased risk of stroke. Although the magnitude was slightly higher and the CI was wider compared to the primary result, which may increase the uncertainty, the association was similar to that obtained in the primary analysis. The present finding is relatively novel because none of the prior reviews investigated the stability of the depression–stroke association over time. My result to a certain extent agrees with the findings from the Pan et al. (2011a) study, which was one of the few that investigated the association between time-dependent depression and stroke. The authors followed up 80,574 women aged between 54 and 79 years without a history of stroke for six years as part of a nurses' health study. Pan et al. (2011a) assessed depression biennially and found that depressed women had a 29% (HR = 1.13, 95% CI, 1.13, 1.48) increased risk of a future stroke. Though obviously their finding was limited to specific gender data and depression in this study was measured using a combination of mixed indictors (antidepressants, clinical diagnosis and SRS). The consistency of the summary effects validates my hypothesis that baseline depression can predict the risk of stroke incidence as well as time-varying depression, although further studies are warranted to confirm this finding.

4.5.3 **Reverse causality**

To explore the impact of possible reverse causation, I restricted the analysis to studies that accounted for residual confounding by excluding the initial follow-up period. The positive significant association became more pronounced (HR = 1.39, 95% CI, 1.11, 1.74) after synthesising this analytic 'lag period' approach based on four cohorts. However, the small study number (n=4) and the moderate heterogeneity between studies (I^2 = 58%) render the results meaningless. Among the past reviews, only Barlinn et al. (2015) assessed for possible reverse causation by adopting the same analytical approach. Their synthesised sub-analysis data consisted of six cohorts and provided similar findings that depression is associated with a 41% increased risk of stroke incidence (HR = 1.41, 95% CI, 1.27–1.57). Nevertheless, one of the included studies in their analysis was ineligible (Pequignot et al., 2013) as it reported an HR for a combined endpoint (fatal and non-fatal CHD or stroke).

4.5.4 **Types of depression assessment tools and stroke**

When comparing different types of assessment methods used to identify depression, my subgroup analysis found a 21% increased risk of stroke incidence for studies that used SRS, which is consistent with the primary results and previous reviews (Barlinn et al., 2015, Dong et al., 2012, Li et al., 2015a, Pan et al., 2011b). However, combining the HR from the seven studies that relied on a clinical diagnosis resulted in a lower estimate (HR = 1.13, 95% CI, 0.98, 1.31), which contradicts the above finding. This result also differed from Li et al. (2015a) and Pan et al. (2011b) meta-analyses which found that patients diagnosed with clinical depression are at a twofold increased risk of a future stroke; however, comparing my results to these reviews is somewhat complicated because both studies enrolled populations with a history of stroke and/or CHD. Nevertheless, this subgroup analysis highlighted some methodological limitations in two of the six studies that failed to detect an association. Sico et al. (2018), the largest study influencing the estimated risk in this subgroup, was a conference abstract that did not contain adequate information, so I was unable to closely assess its quality. Further, Wouts et al. (2008) had a relatively few participants with an MDD at baseline (n = 58), which may have limited the ability to find an association between depression and stroke risk. Nevertheless, the results from the subgroup

cohorts that used clinical diagnosis and/or antidepressants to identify cases of depression demonstrate that depression is associated with a 34% increased risk of stroke incidence. In most cases, depression identified through a structured clinical interview and/or through a valid prescription of antidepressants reflects severe depression status. Thus, this pronounced effect of depression on risk of incident stroke may support a dose-response theory. Alternatively, as these studies used antidepressants as an indicator of depression, it is possible that they suffer from misclassification, and their results may not necessarily reflect the independent association of depression with stroke. Further, statistically, combining different depression indicators can enhance statistical power and thus obtain significant findings. The findings suggest that depressed individuals defined based on the use of antidepressant medication did not have an increased risk of stroke. Similarly, Li et al. (2012), whose study was excluded from this analysis, retrospectively reviewed the pattern of antidepressant prescriptions prior to stroke onset in depressed patients and showed that no clinically relevant associations existed between antidepressants and stroke. This may be a true indication that antidepressants are not associated with an increased risk of stroke in a CVD-free population. However, each individual class of antidepressants has a different safety profile with respect to different CVD outcomes (Hamer et al., 2011, Glymour et al., 2019) and my finding is not informative from this prospect. In contrast to my results, Barlinn et al. (2015) and Pan et al. (2011b) explored the independent effect of antidepressants in a sub-analysis of six studies, and both found that antidepressant medication is associated with an elevated risk of stroke. However, both reviews included cohorts with previous incidences of CHD/stroke, which may explain the possible relationship. A recent nested case-control study of 344,747 individuals showed that antidepressants are significantly associated with an increased risk of stroke in patients who previously suffered from CVD compared to those who did not (Biffi et al., 2020). Although the interpretation is limited by a few included studies and the large heterogeneity between them, the divergent results obtained from this subgroup analysis may indicate that different depression measures tend to have different predictive values for stroke risk, although it is unclear how strongly and how valid each separate approach predicts stroke. Therefore, I conclude that we do not yet have sufficient evidence to determine which type of depression assessment tool is best for predicting stroke risk among depressed individuals in clinical settings and would encourage future

research to examine different measurements or indictors of depression in parallel with this regard.

4.5.5 **Age factor**

I stratified the analysis according to the participants' mean age to investigate the sources of heterogeneity and explore possible modifiers of the depression-stroke relationship. My subgroup showed that no statistically significant association existed between depression and risk of stroke in elderly patients aged 65 years and above (HR = 0.92, 95% CI, 0.67, 1.27). However, younger patients (aged <65 years) were at a significantly greater risk of developing stroke in relation to depression (HR = 1.30, 95% CI, 1.18, 1.42). The test for subgroup differences indicates a marginal statistically significant subgroup effect (p = .05). However, far smaller cohorts and participants contributed data to the subgroup with a mean age of ≥65 years (four cohorts with 18,805 participants) than to the subgroup with a mean age of <65 years (14 cohorts with 3,227,725 participants), meaning that the finding from this subgroup analysis cannot be relied on to produce a valid conclusion. However, this trend has been observed in the past reviews, as both Barlinn et al. and Pan et al. reported a lower risk of stroke in depressed patients aged ≥65 years than in those aged <65 years. In the Framingham Heart Study, Salaycik et al. (2007) examined elderly and non-elderly groups separately and found that depressive symptoms were statistically significantly associated with a fourfold increase in the risk of future stroke in patients younger than 65 years but not in those aged 65 years or older. Some other studies that did not meet my eligibility criteria also proposed similar findings that depression may not be an independent risk factor for stroke in the elderly (Colantonio et al., 1992, Köhler et al., 2013), although other positive findings suggesting a strong association between depression and stroke in this targeted population also exist (Gilsanz et al., 2015, Krishnan et al., 2005, Liebetrau et al., 2008). Polypharmacy is known to be common among elderly individuals. Accordingly, it is highly plausible that some medication prescribed as a primary prevention for stroke, such as antihypertensive medications, may mask the effect of depression on stroke. Frasure-Smith and Lesperance (2006) summarised evidence linking depression and cardiac disease. The authors suggested an alternative interpretation that might also be applicable to stroke outcomes. They proposed that a group of individuals

who managed to achieve more than 80 years without CVD manifestation are likely to be both genetically and behaviourally advantaged in some way compared to most individuals. Although the result from this analysis was not very useful to draw a clinically meaning conclusion with respect to the age factor, it calls for future studies to investigate the pathological mechanism linking depression to stroke in the young population with no known history of stroke or cardiac diseases and to determine whether late-life depression can be considered a true risk factor for incident stroke in this elderly population.

4.5.6 **Depression and risk of stroke subtype**

Analysing studies by stroke subtypes showed that depression is associated with an increased risk of ischemic stroke (HR = 1.16, 95% CI, 1.02, 1.31) but not haemorrhagic stroke (HR = 1.09, 95% CI, 0.98, 1.22), although no statistically significant subgroup effect exists (p = .41). Although interpretation is limited by the lack of sufficient numbers in each subgroup, these findings are in line with reviews by Li et al. (2015a) and Pan et al. (2011b), which showed no statistically significant association between depression and haemorrhagic stroke (HR = 1.16, 95% CI, 0.80,1.70). Their results derived from two studies (Pan et al., 2011a, Ohira et al., 2001) enrolling 1,912 participants. The results herein were also pooled from two cohorts, albeit with a much larger sample size (2,418,715). Several studies have shown that each stroke subtype is likely to have a different risk factor profile (Price et al., 2018, Hägg et al., 2014, Zhang et al., 2011). Future studies investigating whether depression imposes different effects across stroke subtypes and the possible mechanisms by which depression is linked to different stroke subtypes are needed.

4.5.7 **Comparison with other reviews**

Although the main finding is consistent with previous meta-analyses in terms of the direction of the estimated risk, the magnitude of the pooled adjusted HR in the current study was about half that of the estimated risk in past reviews (Barlinn et al., 2015, Dong et al., 2012, Li et al., 2015a, Pan et al., 2011b, Van der Kooy et al., 2007), which ranged from 35% to 45%. Nevertheless, the quantified risk of depression in my study is similar to the findings from a recent large prospective cohort conducted by Cho et al. (2019) in South Korea. Cho et al. (2019) used

nationwide health insurance claims data to enrol 2,705,090 participants who were free of stroke and CHD at baseline and found that depression was associated with a 24% (HR = 1.24, 95% CI, 1.21-1.27) increased risk of first-ever stroke. However, the risk is likely to differ across different populations. In a multicentre cohort involving 145,862 participants from 21 economically diverse countries, Rajan et al. (2020) showed that adults with four or more depressive symptoms were at a 20% higher risk of death and developing a cardiovascular event compared to people without depressive symptoms, although the risk was more than twice as high in urban areas as in rural areas. Wium-Andersen et al. (2020) recruited participants from 10 Danish population-based cohorts studied between 1981 and 2015 and suggested that depression increased the risk of first-ever stroke by 94% (HR = 1.94, 95% CI, 1.63, 2.30). The following section provides a detailed description and critical appraisal of past reviews. As previously stated, Van der Kooy et al. (2007) published the first review on this subject, although they evaluated and quantified the risk of depression on stroke incidents as a secondary analysis. The reviewer included both case-control and prospective cohort studies that were published before 2005. Pooling the effect size from 10 studies showed that depression is associated with a 43% increased risk of stroke onset (OR = 1.43, 95% CI, 1.17, 1.75, I^2 = 45%). Notably, in the case of stroke outcomes, the case-control study design is not the proper design to obtain information on prior depressive episodes because stroke victims may suffer from serious complications, such as cognitive dysfunction, making them vulnerable to recall bias, which results in imprecise findings. In 2011, Pan et al. (2011b) updated and enlarged the earlier work with a primary focus on stroke outcomes. They searched three databases, including MEDLINE, EMBASE and PsychINFO. Only prospective cohort studies were eligible with participants either with or without a history of stroke. Eventually, they ended up with 28 studies enrolling 317,540 participants. The quality assessment in this review was performed based on eight aspects, including study design, response rate, follow-up rate, follow-up years, exposure and outcome measurements, statistical analysis, and generalisability to other populations, which are comparable with the NOS tool assessment criteria. The primary result of their meta-analysis demonstrated that depression significantly increased the risk of stroke development by 45% (HR = 1.45, 95% CI, 1.29, 136) with a considerable statistical heterogeneity (I^2 = 66%). The relatively larger number of included studies compared to the previous review enabled Pan et al. (2011b) to

test the association in further subgroup analyses and showed a consistent positive association across different subgroups. The reviewers demonstrated that no statistically significant differences existed between studies that excluded past stroke cases and those that did not (p =.21). Nevertheless, since there was uneven covariate distribution arising from the unbalanced number of studies across this subgroup (24 studies vs 7 studies), the validity of their results is restricted. Dong et al. (2012) carried out a subsequent review with stricter inclusion criteria. The authors used only one search engine, PubMed database, to obtain potentially relevant studies. Only population-based studies enrolling stroke-free participants with a prospective cohort design were included. However, owing to the limited number of database resources, the authors omitted several eligible studies (Avendano et al., 2006, Arbelaez et al., 2007, Kawamura et al., 2007, May et al., 2002, Stürmer et al., 2006). Further, this publication did not supplement readers with the quality assessment of the included studies; hence, it is difficult to determine the burden of study quality to compare with my review. A total of 17 cohorts involving 206,641 participants were ultimately included. The pooled effect size demonstrated that participants with depressive symptoms experienced a 34% (HR = 1.34, 95% CI, 1.17, 1.54) higher risk for developing a stroke event with moderate statistical heterogeneity (I^2 = 55%, p = .003). Notably, the risk estimate reported by this review was the lowest compared to four reviews answering the same research question (Van der Kooy et al., 2007, Li et al., 2015a, Barlinn et al., 2015, Pan et al., 2011b). Li et al. (2015a) performed the largest review to date on this subject. The reviewers used three databases, including PubMed, Embase and the Cochrane Library, to identify 36 studies enrolling 399,791 participants. Quality assessment of the included articles was based on the guideline developed by the US Preventive Task Force, which is composed of eight criteria resembling those in the NOS assessment tool. The pooled risk estimate demonstrated that depression was associated with a 45% increased risk of stroke onset (HR = 1.45, 95% CI, 1.31, 1.61) – a considerable statistical heterogeneity was detected between studies (I^2 = 66%, p < .000). Around the same time, Barlinn et al. (2015) published a similar review but with stricter inclusion criteria, as their search primarily focused on the stroke-free population. They searched PubMed and Medline for eligible studies. However, as the Medline database is a subset of PubMed database (≈98%) (Williamson and Minter, 2019), the output is greatly similar. To achieve an acceptable recall, a combination of four databases is recommended (Bramer et

al., 2017), in addition to using the PsycINFO database, which provides unique references to this relevant topic. Barlinn et al. identified 28 eligible studies with 681,139 participants. The assessment of the methodological quality of the included studies was performed in accordance with the NOS tool. Although Barlinn et al. adopted stricter inclusion criteria than Li et al., their quantified estimated risk was comparable (HR = 1.40, 95% CI, 1.27, 1.53, I^2 = 48.6%). Compared to the other reviews, Barlinn et al. was the only review that also performed a sensitivity analysis, restricting the data synthesis to 15 studies excluding cardiac patients; however, their pooled risk estimate was 43% (RR = 1.43, 95% CI, 1.19–1.72), which was similar to their main result.

In my study, I updated the review conducted by Van der Kooy et al. (2007), which covered a search period up to 2005. Thus, the period of my study considered only studies published after 2004. I employed a similar search strategy to Pan et al.'s review, although I also searched the Web of Science database and hand-searched the bibliography of related reviews and all relevant articles. Additionally, I extended the search to July 2020. The selection criteria in my review were modified based on the conclusion and recommendations of the latest review conducted by Barlinn et al. (2015) to reduce heterogeneity and risk of bias. Briefly, two aspects were not considered in the past reviews that may influence the estimated risk of depression: types of population and a clear definition of acceptable measures of depression. In terms of the population, the majority of past reviews did not focus on a stroke-free population (Li et al., 2015a, Pan et al., 2011b, Van der Kooy et al., 2007) and did not consider the role of the other vascular comorbidities such as cardiac disease in the depression-stroke relation, which can increase the possibilities of reveres causality or exaggerate the effect of depression on stroke outcome. In terms of exposure measures, none of the past reviews clearly defined how clinically related depression symptoms should be measured for a study to be eligible (Barlinn et al., 2015, Dong et al., 2012, Li et al., 2015a, Pan et al., 2011b, Van der Kooy et al., 2007). They combined depression data, which were presented as either binary or ordinal variables. For example, if the studies categorised depressed individuals as having low, moderate or severe depressive symptoms based on the SRS (Kamphuis et al., 2006, Stürmer et al., 2006, Vogt et al., 1994), they considered only those individuals with high or severe symptoms. This approach is likely to be subjected to selection bias.

Further, as this approach is not equivalent to the binary dichotomous response to SRS thresholds or to clinical diagnosis, it may have affected the consistency of the reported risk and the accuracy of their estimated effect. My inclusion criteria are narrower compared to all reviews on this topic, as I only included studies that enrolled patients with no known history of stroke and CHD at baseline and I attempted to minimise the impact of selection bias on the estimated risk by including studies that clearly defined depression as a dichotomous variable where participants were classified as depressed and not depressed. I used a similar approach to Barlinn et al. to assess the methodological quality of each included cohort. My review is composed of fewer studies, 19 studies, compared to previous reviews, which may in part explain the lower estimated risk. However, I included seven new prospective cohorts (Daskalopoulou et al., 2016, Jee et al., 2019, Li et al., 2019, Mathur et al., 2016, Moise et al., 2016, Karlsen et al., 2020, Rajan et al., 2020) with larger sample sizes than previous reviews, adding more than 3,000,000 participants, thus substantially increasing the power. Further, I identified two studies (Krishnan et al., 2005, Mejia-Lancheros et al., 2014) that were omitted by recent reviews. Ten studies (Arbelaez et al., 2007, Avendano et al., 2006, Glymour et al., 2010, Hamano et al., 2015, Jackson and Mishra, 2013, Kamphuis et al., 2006, Liebetrau et al., 2008, Pan et al., 2011a, Salaycik et al., 2007, Surtees et al., 2008b) published after 2004 and included in the latest review were excluded from my study for reasons described in Section 3.2.1. Therefore, to my knowledge, the present meta-analysis includes all qualified studies, including those omitted by previous meta-analyses and most recent studies assessing the effect of depression on risk of incident stroke.

4.6 Conclusion

Overall, evidence from this study shows that baseline depression is associated with elevated risk for new-onset stroke in patients with no known history of CHD and stroke. Similarly, a positive association was also observed for depression assessed over time. Future studies should investigate whether age modifies the relation between depression and stroke and, if so, the pathological mechanisms underlying early and late-life depression leading to stroke. Further, more studies are warranted to examine whether depression confers a greater risk for ischemic stroke than for haemorrhagic stroke.

5 Depression and risk of CHD first event: An updated systematic review and Meta-analysis

5.1 Introduction

5.1.1 CHD prevalence and burden

In 2015, CHD was reported to be the leading cause of death worldwide accounting for 9 million deaths (Roth et al., 2017). The estimated age-standardised CHD death rate was highest in Central Asia (336 per 100,000) and Eastern Europe (326 per 100,000). Further, there were an estimated 110.55 million prevalent cases of CHD and 7.29 million acute MI in 2015. Eastern Europe had the highest estimated age standardised prevalence of CHD (4,140 cases per 100,000) followed by Central Asia and then Central Europe, while the sub-Saharan Africa, southern Latin America and high-income Asia Pacific regions had the lowest estimated rate (622 per 100,000) (Roth et al., 2017). In 2017, it was estimated that more than 126 million people were living with CHD, and it was more prevalent in males than in females. Mortality rates were generally lower than 150 per 100,000 for most of the world but remain the highest in Eastern Europe and Central Asia (Virani Salim et al., 2020). According to a recent statistical report by the AHA, a decline in the incidence of CHD has been observed over the past decades; however, the number of cases is projected to increase because of population ageing, which means that CHD will continue to be a leading cause of death and prevention of CHD should be a continuing priority (Benjamin et al., 2019). Several prevention approaches have been put forward to reduce the incidence of CHD. Potential strategies include controlling and addressing risk factors to reduce the risk of developing CHD and make significant health gains. Risk factors associated with an increased risk of CHD involve nonmodifiable risk factors, such as age, gender, family history and race, and modifiable risk factors, such as hypertension, smoking, sedentary lifestyle, abnormal lipid profiles, inflammatory markers, diabetes and metabolic syndrome (Khawaja et al., 2009). Additionally, evidence shows that psychological factors, such as depression, can be as big a risk factor for CHD as smoking, high cholesterol levels and high BP (Dhar and Barton, 2016).

5.1.2 Bidirectional relationship between depression and CHD

5.1.2.1 Depression and established CHD

Numerous studies have reported the prevalence of major depression or clinically significant depression in patients with established CHD (Carney and Freedland, 2017). In a comprehensive review, Thombs et al. (2006) proposed that depression is about three times more common in patients recovering from an acute MI than in the general population. An estimated 15% to 20% of patients hospitalised after MI found to meet the DSM-diagnostic criteria for MDD (Lespérance and Frasure-Smith, 2000) with an even greater proportion (40%) of patients reporting elevated levels of depressive symptoms (Bush et al., 2005). Spijkerman et al. (2005) reported that a history of MI is an independent predictor of both in-hospital and post-discharge depressive symptoms. Together, these findings suggest that CHD can cause depressive symptoms and depression following MI (Khawaja et al., 2009, Spijkerman et al., 2005). Research has extensively documented the association between depression and poor health prognosis in patients with established CHD. As noted above, depression is highly common in post MI patients and it has been linked to recurrent cardiac events (van Melle et al., 2004), cardiac-related death (Frasure-Smith et al., 1993, van Melle et al., 2004, Whang et al., 2009) and all-cause mortality (Barth et al., 2004, van Melle et al., 2004). These links prompted the AHA to elevate depression to the status of a risk factor for adverse medical outcomes within this population (Lichtman et al., 2008).

5.1.2.2 Depression as a risk factor for CHD incident

Studies have also found that depression increases the risk of cardiac events in people without a history of CHD. So far, six meta-analyses have evaluated depression as a risk factor for incident CHD (Table 5-1). The main objective of these studies was to quantify depression risk. Main limitations and detailed description of the past six previous reviews were discussed in section 5.6.7 of the current chapter. Briefly, past reviews relied on studies that were poorly designed. This was not surprising given that the depression-CHD hypothesis was relatively young in the last century compared to established risk factors for CHD such as smoking (Nicholson et al., 2006). Thus, complex interplay between depression and CHD had not considered. Therefore, I aimed to update and elaborate previous

work on depression-CHD relation by conducting a systematic review and meta-analysis of cohort studies.

5.2 Aim

By performing a systematic review and meta-analysis of cohort studies, this chapter aims to establish whether an independent association with CHD exists for depression (either measured at baseline or at multiple instances) within a study population that is free of both CHD and stroke disease.

5.3 Hypotheses

1- Depression is associated with an increased risk of incident CHD in patients with no history of CHD or stroke.

2- Depression increases the risk of CHD incidence in a dose-response manner.

3- Baseline depression predicts future CHD as equally well as depression measured on a multiple instant.

Table 5-1 Summary of meta-analysis examined depression as a risk factor for CHD incident

Meta-analysis	Search period	K	N	Outcomes					
				Combined events of CHD		MI		CHD death	
				N	OR/RR (95%CI)	N	OR/RR (95%CI)	N	OR/RR (95%CI)
(Rugulies, 2002)	1887-2000	11	36,549	11	1.64 (1.29–2.08)	NA	NA	NA	NA
(Wulsin and Singal, 2003)	1966-2000	10	27,231	10	1.64 (1.41,1.90)	NA	NA	NA	NA
(Nicholson et al., 2006)	1966–2003	21	124 509	11+	1.90 (1.49–2.42)	NA	NA	9	1.69 (1.34–2.14)
(Van der Kooy et al., 2007)	1966-2005	28	87,174	16*	1.57 (1.36–1.81)	8	1.60 (1.34–1.92)	NA	NA
(Gan et al., 2014)	Up to 2014	30	893 ,850	30	1.30 (1.22,1.40)	12	1.30 (1.18,1.44)	8	1.36 (1.14, 1.63)
(Wu and Kling, 2016)	1966-2015	19	323,709	16*	1.20 (1.11–1.30)	9	1.31 (1.09–1.57)	8	1.36 (1.14–1.63)

CHD, coronary heart disease; CI, confidence interval; K, nnumber of studies; MI, myocardial infarction; N, number of participants; NA, not applicable; RR, risk ratio; OR, odds ratio;*Includes only those studies of participants without CHD at baseline. +Adjusted analyses.

5.4 Methodology

5.4.1 Search strategy and selection criteria

Section 2.1 provided full descriptions of the methods used for this systematic review and meta-analysis, and Chapter 3 described the risk of bias of studies included in this review.

5.4.2 Statistical analysis and data synthesis

Overall, I used the HR as the parameter of interest to study the association between depression and CHD. One study that used RR to report the estimated risk was excluded from the primary analysis for consistency. For the primary analysis, two studies provided HRs for women and men separately (Ladwig et al., 2006b, Jee et al., 2019). I obtained a study level HR by pooling risk estimates from both groups to obtain a single overall estimate. Where studies reported HRs for multiple CHD events, I pooled only one HR corresponding to the largest number of the multiple events (however, the other HRs were included in the subgroup analysis).

Sensitivity analyses assessed the contribution of each study to the pooled estimate by excluding individual studies one at a time and re-calculating the pooled HR for the remaining studies (so-called 'one-study removed meta-analysis'). Further exclusion was performed to exclude studies that had (1) not controlled for confounders, (2) enrolled participants with a high risk of developing CHD and (3) employed tools or diagnostic criteria that failed to clearly discriminate between different depressive disorders. I also restricted the analysis to studies that had excluded CHD events occurring within the first year of follow-up, which provided HRs for depression risk measured at multiple time points (i.e. depression modelled as a time-varying covariate) and that were looking for a first event of stroke or CHD outcomes within the same cohort.

5.5 Results

My search identified 23 eligible studies that reported CHD outcomes enrolling 3,786299 patients with an average follow-up of 12.4 years (range 4 to 37 years).

Table 5-2 shows the main characteristics of the 23 cohorts included in this review, encompassing the first author's name and year of publication, total number of participants enrolled, proportion of males, mean age, mean or median duration of follow-up (where applicable), methods used to measure exposure (depression), main outcomes, methods used to identify outcomes, total number of cases and covariates that were adjusted within the multivariable analysis. The largest cohort was the one conducted by Daskalopoulou et al. (2016), followed by Mathur et al. (2016) and Jee et al. (2019). While The smallest study was conducted by Gafarov et al. (2013) with a sample size of 560. With regard to study location, most studies were conducted in European countries (n = 13), eight in the United States, one in Korea, and one was a multinational cohort. Gender ratios varied considerably between cohorts. Seven studies enrolled mainly male participants (>60%) (Brunner et al., 2014, Gump et al., 2005, Janszky et al., 2010, Karlsen et al., 2020, Khambaty et al., 2014, Majed et al., 2012, Scherrer et al., 2011) and four other cohorts included predominantly females (Brown et al., 2011, Gafarov et al., 2013, Pequignot et al., 2013, Whang et al., 2009). Depression screening was largely based on self-rating scales (n = 14). Two studies also used antidepressant prescriptions as a proxy for depression (Nabi et al., 2010a, Whang et al., 2009). The CES-D scale was used in nine cohorts; the other six studies each used a different scale. The remaining nine studies relied on clinical diagnosis based on ICD or DSM criteria. However, four studies also included patients with antidepressant medication (Daskalopoulou et al., 2016, Mathur et al., 2016, Rahman et al., 2013, Scherrer et al., 2011). A total of 26 reports were extracted from the included cohorts. Of those, 11 reported CHD outcomes associated with depressive symptoms as a combined endpoint, 13 reported incidence of MI, two reported incidence of angina (Daskalopoulou et al., 2016, Jee et al., 2019) and two reported CHD death (Daskalopoulou et al., 2016, Whang et al., 2009). The number of CHD cases diagnosed in the primary studies ranged from 15 to 23,735, with a total of 69,808 cases. Outcome ascertainment was from a variety of sources, including medical records, register databases, National Death Index, clinical diagnoses and death certificates. Apart from Brunner et al. (2014), Gafarov et al. (2013), the majority of the included studies adjusted for the pre-specified confounding factors (see section 2.1.5). All studies calculated the effect estimate using HRs, except for one study that reported RR (Brown et al., 2011).

Table 5-3 summarises additional information for the 23 included cohorts, encompassing the first author's name and year of publication, type of population, number of depression assessments over the study period and whether studies provided an additional analysis for the following: after excluding CHD events that occurred during first year of follow-up, severity/chronicity of depression and risk of CHD, independent association of antidepressants and risk of CHD, and proportion of patients who were lost to follow-up. All included studies defined their population as free of CHD and stroke at baseline. Two studies also excluded hypertensive patients (Gafarov et al., 2013, Scherrer et al., 2011). Three studies examined the association between depression and CHD in comorbid populations such as obese (Ladwig et al., 2006b), diabetic (Scherrer et al., 2011) and HIV patients (Khambaty et al., 2016) . Some studies (n = 6) excluded CHD events occurring in the first year of follow-up to reduce reverse causation (Gustad et al., 2014a, Majed et al., 2012, Nabi et al., 2010a, Péquignot et al., 2016, Karlsen et al., 2020). Nine studies assessed whether a dose-response relationship existed between depression severity/chronicity and CHD, but with different methods (Brown et al., 2011, Brunner et al., 2014, Gustad et al., 2014a, Jee et al., 2019, Nabi et al., 2010a, Péquignot et al., 2016, Whang et al., 2009, Wulsin et al., 2005, Gump et al., 2005, Rajan et al., 2020). Five studies used the severity of depressive symptoms (i.e. higher score vs lower scores on the SRS), while the other four measured depression chronicity (i.e. how many times patients presented with clinically important depressive symptoms) during the follow-up period before the index date. Five studies measured depressive symptoms at multiple time points in addition to baseline, and treated depression as a time-dependent variable in their analyses (Moise et al., 2016, Péquignot et al., 2016, Whang et al., 2009, Brunner et al., 2014). Five studies investigated the independent association between antidepressants and CHD (Mathur et al., 2016, Nabi et al., 2010a, Rahman et al., 2013, Scherrer et al., 2011, Whang et al., 2009). Finally, loss to follow-up ranged from nil to 8%, although one reported a 28% loss to follow-up, and 10 studies failed to report on this aspect.

Table 5-2 Characteristics of the included cohort studies

Study	Location	N	Men (%)	Age (years)	Length of follow-up (years)	Exposure measure	Outcome	Outcome measure	Cases (n)	Confounder adjustment
(Brown et al., 2011)	US	2,728	28.6	60-102	15 years 1991-2006	20-item CES-D ≥16	MI and CHD death	Medical record, NDI (ICD-9 codes 410–414 and ICD-10 codes 120–125)	727	Age, sex race, diabetes, HTN, history of smoking, cholesterol, and ideal body weight
(Brunner et al., 2014)	UK, EU	10036	67	35-55	24 years 1985-2009	GHQ-30 ≥ 5	Fatal CHD/non-fatal MI	Self-reported confirmed be using medical records, GP confirmation and death certificate (ICD-9 codes 410–414 or ICD-10 codes I20– I25)	454	Age, sex, and ethnicity
(Daskalopoulou et al., 2016)	UK, EU	1,937,360	NA	≥30	13 years 1997-2010	Medical records of CD and/or prescription of AD	Stable angina, unstable angina, MI, and unheralded CHD death	Medical records (ICD-10 codes 120–125)	23735	Age, sex, smoking, SBP, diabetes, cholesterol, and socio-economic status
(Davidson et al., 2009)	Canada	1,794	49.9	18-98	10 years 1995-2005	20-item CES-D ≥10	Fatal/non-fatal CHD	Health register records (ICD-9 codes (410.–414 or the equivalent on ICD-10)	152	Age, gender, and Framingham risk score
(Gafarov et al., 2013)	Russia	560	0	25-64	16 years, 1995-2010	15-item MOPSY (subscale depression) questionnaire	MI	Medical records and death certificates	15	Age
(Gump et al., 2005)	US	11,216	100	46	18.4 years	20-item CES-D ≥13	Fatal CHD and MI	Death certificate according to the ICD-9 codes	1248	Age, intervention group, race, educational attainment, smoking at baseline and visit 6, trial averaged SBP, alcohol consumption, and fasting cholesterol, as well as the occurrence of nonfatal cardiovascular events during the trial
(Gustad et al., 2014a)	Norway, EU	57,953	45.8	47.7	11.4 years 1995-2008	HADS-D ≥11	Fatal/non-fatal MI	Clinical diagnosis, death registry (ICD-9 codes 410 and ICD-codes I21- I22).	2,111	Age, sex, marital status, education, smoking, physical activity, BMI, total cholesterol, diabetes mellitus and SBP

Study	Location	N	Men (%)	Age (years)	Length of follow-up (years)	Exposure measure	Outcome	Outcome measure	Cases (n)	Confounder adjustment
(Hamieh et al., 2019)	France, EU	10,541	74.5	47.8	20 years 1994-2014	20-item CES-D ≥17/23	Non-fatal CHD	Medical records or self-reported confirmed by medical records	592	Age, sex, HTN, diabetes, dyslipidemia, occupational grade, parental CHD history, obesity, smoking status and physical inactivity.
(Janszky et al., 2010)	Sweden, EU	49,321	100	18-20	37 years 1969- 2006	Structured interview by a psychologist and classified according to the (ICD-8; 29,300.4)	CHD, MI	Medical records	52	Smoking, body length, diabetes, SBP, alcohol consumption, physical activity, father's occupation, family history of CHD, and geographic area
(Jee et al., 2019)	Korea	481,355	54.15	52.8	13 years 2002-2013	≥ 1 out-patient visit diagnosed according to (ICD-10 codes F32-F33) or prescription of AD at >3 out-patients visits	Fatal/ non-fatal CHD, angina, MI	Mediacl records	16915	Age, smoking status, HTN, hypercholesterolaemia, diabetes and chronic renal failure
(Karlsen et al., 2020)	US	3135	100	76.38	12 years 2003-2015	9-item GADS ≥2	Fatal and non-fatal CHD	Tri-annual questionnaire and/or phone conformed by medical records. Fatal event adjudicated by death certificate, hospital record or next of kin interview	612	Age, education, race/ethnicity, diabetes, AD use, BMI, cholesterol/oxidised LDL, smoking status, drinking habit, physical activity and sleep quality

Study	Location	N	Men (%)	Age (years)	Length of follow-up (years)	Exposure measure	Outcome	Outcome measure	Cases (n)	Confounder adjustment
(Khambaty et al., 2016)	US	26,144	97.3	≈48	11 years 1998-2009	Diagnosed according to ICD-9	MI	Medical records, death certificate (ICD-9 code 410 for MI)	490	Age, sex, race/ethnicity, HTN, dyslipidaemia, diabetes, statin use, CD4 cell count, HIV-1 RNA level, antiretroviral therapy regimen, hepatitis C infection, renal disease, history of abuse or dependence of alcohol and cocaine, and haemoglobin level Smoking, BMI, anti-depressants
(Ladwig et al., 2006b)	Germany, EU	6,239	51.8	45 -74	7.1 years (mean) 13.7 Max	24-item-DEEX scale	MI and CHD	Medical records, death certificates (ICD-9, 410–414, 798)	229	Age, total cholesterol, cigarette smoking and SBP, education, alcohol consumption and physical activity
(Majed et al., 2012)	France, Ireland, EU	9,601	100	48-64	10 years (median) From 1991	Fourth quartile of 13-item-modified CES-D compared with first quartile	CHD (stable and unstable angina, MI, and coronary death)	Hospital or general practitioner records According to clinical, biological, stress-test, scintigraphic, or angiographic criteria	647	Age, study centres, socioeconomic factors, including marital status, education level, employment status, physical activity, smoking status, daily alcohol intake, SBP, use of anti-hypertensive drugs, BMI, total and HDL cholesterol, treatment for diabetes, and use of AD

Study	Location	N	Men (%)	Age (years)	Length of follow-up (years)	Exposure measure	Outcome	Outcome measure	Cases (n)	Confounder adjustment
(Mathur et al., 2016)	UK, EU	524,952	52.8	≥30	10 years 2005- 2015	CD, read code used in general practice across the UK	MI	Clinically diagnostic Read code used in general practice across the UK	3,390	Age, sex, and ethnic group, diabetes, HTN, hyperlipidaemia, and smoking AD prescribing at baseline, obesity, and Townsend deprivation score, presence of co-morbid anxiety
(Mejia-Lancheros et al., 2014)	Spain, EU	7,263	42.5	55-80	7 years 2003-2010	Self-reported by face to face interview and further confirmed in clinical records According to the DSM-IV or other mental health scales BDI	MI	Regular contacts with participants and/or families, annual revisions of medical records, data from GPs, and consultation of the NDI	103	Age, sex, smoking, alcohol consumption, BMI, HTN, type 2 diabetes, dyslipidaemia and family history of premature CHD, and type Mediterranean diet intervention

Study	Location	N	Men (%)	Age (years)	Length of follow-up (years)	Exposure measure	Outcome	Outcome measure	Cases (n)	Confounder adjustment
(Moise et al., 2016)	US	22,666	41.2	≥45 years	9 years 2003-2012	4-item-CES-D ≥4	CHD events (nonfatal or fatal MI or acute CHD death events)	Self-administered questionnaires with retrieval of medical records	895	Age, sex, region, income, health insurance, education, and traditional CHD risk factors (SBP, total cholesterol, HDL- cholesterol, and medication use [aspirin, statins, any antihypertensive medications], BMI, log of albumin: creatinine ratio, diabetes mellitus, pack-years of cigarette smoking, self-reported alcohol use, physical inactivity, medication adherence, log of high-sensitivity C-reactive protein, AD use, QT interval corrected for heart rate, atrial fibrillation and left ventricular hypertrophy
(Nabi et al., 2010a)	Finland, EU	23, 282	40.8	20-54	7 Years (1998-2005)	21-item-BDI ≥10	Fatal and non-fatal CHD	Hospital discharge register or mortality reports according to (ICD-10 codes I20–I25)	203	Age, sex, education, alcohol consumption, sedentary lifestyle, smoking, obesity, HTN, diabetes and incident CHD or incident CBVD
(Péquignot et al., 2016)	France, EU	7,313	36.6	≥65 (73) mean	10 years	20-itemCES-D ≥16	CHD (angina, MI, and CHD death)	Self-reported further confirmed by medical reports, interviews with the patient's physician or family, death certificates and autopsy reports. All possible event were adjudicated by two independent expert committees (according ICD-10 codes I20-I25; I46.1)	384	Age, gender, city, education level (>12 years), living alone, current smoking,>3 glasses of alcohol a day, diabetes mellites, HTN, hypercholesterolemia, MMSE (Mini Mental State Examination) at baseline examination

Study	Location	N	Men (%)	Age (years)	Length of follow-up (years)	Exposure measure	Outcome	Outcome measure	Cases (n)	Confounder adjustment
(Rahman et al., 2013)	EU	36,654	44.4	63	4 years 2006-2009	National patient registers of psychiatrist diagnosis of depression according to ICD-7	CHD	National patient register, hospital discharge; death certificates (ICD-10 codes I20, I22)	850	Age, sex, smoking status, educational level, HTN, diabetes, alcohol intake and BMI
(Rajan et al., 2020)	Multinational	145,862	58	35-70	14 years 2005-2019	Short form of the CIDI-SF; cut-off point 4 or more depressive symptoms	Fatal/non-fatal MI	Self-reported through standardised form, household interviews, medical records, death certificates, and other sources(according to ICD-10 I60- I64, I69)	3235	Age, sex, urban/rural residence, educational attainment, use of statins, disabilities former and current smoking and alcohol use, HTN, diabetes, and social isolation index
(Scherrer et al., 2011)	US	345,949	88.3	25-80	7 years 2000-2007	CD according to ICD-9	MI	Medical records and register database (according to ICD-9 410–411)	11,659	Age, sex, race, marital status, and insurance type

Study	Location	N	Men (%)	Age (years)	Length of follow-up (years)	Exposure measure	Outcome	Outcome measure	Cases (n)	Confounder adjustment
(Whang et al., 2009)	US	63,469	0	30-55	8 years from 1996-2004	5-item-MHI <53, use of AD	Fatal CHD, non-fatal MI	Medical records, death register or autopsy (according ICD-9 codes 410- 412)	1,724	Age, beginning year of follow-up, smoking status, BMI, alcohol intake, menopausal status and postmenopausal hormone use, usual aspirin use, multivitamin use, vitamin E supplement use, hypercholesterolemia, family history of MI, history of stroke, n-3-fatty acid intake (quintiles), alpha linoleic acid intake (quintiles), and moderate/vigorous physical activity, non-fatal CHD during follow-up, HTN and diabetes
(Wulsin et al., 2005)	US	3,634	45	30-91	6 years (a mean of 5.9)	20-item CES-D ≥16	CHD (MI and CHD death)	Medical records	83	Age, sex stratified, smoking, HTN, diabetes, BMI, total cholesterol, and alcohol consumption

Abbreviations: AD, antidepressants; BDI, Beck's Depression Inventory; BMI, body mass index; BP, blood pressure; CBVD, cerebrovascular diseaseCD, clinical diagnosis; CES-D, Centre for Epidemiological Studies Depression scale; CHD, coronary heart disease; CHF, congestive heart failure; CIDI-SF; Composite International Diagnostic Interview- short form; DEEX, The DEpression and EXhaustion subscale; DBP, diastolic blood pressure, DIS, diagnostic interview schedule; DSM, Diagnostic and Statistical Manual of Mental Disorders;; EU, Europe; GADS; Goldberg Anxiety and Depression Scale; GDS, Geriatric Depression Scale; GHQ, General Health Questionnaire; GP, general practitioner; HDL, high density lipoprotein, HIV, human immunodeficiency virus; HTN, hypertension; ICD, International Classification of Diseases; LDL, low density lipoprotein; MI, myocardial infarction; MHI, Mental Health Index; MOPSY; MONICA-psychosocial programme; NDI, National death index; SBP, systolic blood pressure; UK, United Kingdom; US, United States.

Recently published studies that were not included in previous meta-analysis are shaded

Table 5-3 Selected characteristics from eligible studies

Study	Type of population	Frequency of measuring depression over study period	Lag period	Assessed dose-response relationship/ type of parameter	Examined independent association between AD and CHD	Loss to follow-up (%)
(Brown et al., 2011)	Free of CVD	Baseline	No	Yes Symptoms severity / Cut-off points on CES-D <16, 16-23, ≥24	No	NR
(Brunner et al., 2014)	Free of CHD and stroke‡	Six waves	Yes	Yes Frequency of being an GHQ-30 case	No	0.1
(Daskalopoulou et al., 2016)	Free of CVD	Baseline	No	No	No	NR
(Davidson et al., 2009)	Free of CVD	Baseline	No	No	No	0
(Gafarov et al., 2013)	Free of CHD, stroke, HTN and diabetes mellitus	Baseline	No	No	No	NR
(Gump et al., 2005)	Free of CHD and stroke but who had above average risk of CHD	Baseline	No	Yes/ points on CES-D divided into quintiles 0-1 2-4 5-7 8-12 13-60	No	0
(Gustad et al., 2014a)	Free of CHD and stroke	Baseline	Yes	Yes/ chronicity*	No	28
(Hamieh et al., 2019)	Free of CVD	Seven waves	No	No	No	NR
(Janszky et al., 2010)	Free of CVD	Baseline	No	No	No	NR
(Jee et al., 2019)	Free of CVD	Baseline	Yes	Yes/Number of outpatients visit due to depression	No	0
(Karlsen et al., 2020)	Osteoporosis patients free of CVD	Baseline	Yes	No	No	NR
(Khambaty et al., 2016)	HIV-infected free of CVD	Baseline	No	No	No	NR
(Ladwig et al., 2006b)	Obese free of CHD, stroke and cancer	Baseline	No	No	No	0
(Majed et al., 2012)	Free of CHD and stroke	Baseline	Yes	No	No	0
(Mathur et al., 2016)	Free of CHD and stroke	Baseline	No	No	Yes	0

Study	Type of population	Frequency of measuring depression over study period	Lag period	Assessed dose-response relationship/ type of parameter	Examined independent association between AD and CHD	Loss to follow-up (%)
(Mejia-Lancheros et al., 2014)	Individuals at high risk but free of CVD	Baseline	No	No	No	NR
(Moise et al., 2016)	Free of CVD	Three waves	No	No	No	1.6
(Nabi et al., 2010a)	Free of CHD and stroke	Baseline	Yes†	Yes Symptoms severity / Cut-off points on BDI, 0-9, 10-18 19-29 30-63	Yes	0
(Péquignot et al., 2016)	Free of CHD and stroke	Four waves	Yes**	Yes Frequency of being CES-D case	No	8%
(Rajan et al., 2020)	Free of CVD	Baseline	Yes	No	No	2
(Rahman et al., 2013)	Free of CVD	Baseline	No†	No	Yes	NR
(Scherrer et al., 2011)	Diabetic free of psychotic disorders and bipolar disorder, HTN and CVD at baseline	Baseline	No	No	Yes	NR
(Whang et al., 2009)	Free of CHD, stroke or cancer	Three waves	No	Yes/ Cut-off points on MHI-5, 0-52, 53-75 76-8	Yes	NR
(Wulsin et al., 2005)	Free of CVD, dementia and cancer	Baseline	No	Yes Symptoms severity/ CES-D tertials Low Medium High	No	0.05

BDI, Beck's Depression Inventory; CES-D, Centre for Epidemiological Studies Depression scale; CHD, coronary heart disease ; CVD; Cardiovascular diseases; HTN, hypertension; GHQ, General Health Questionnaire HIV, human immunodeficiency virus ; MHI, Mental Health Index. * Data calculated for mixed symptoms of depression and anxiety, ** Data presented only for a combined fatal event (CHD or stroke); † Data not provided, ‡ Information extracted from Barlinn et al. (2015) and Gan et al. (2014)

5.5.1 Depression and risk of CHD

5.5.1.1 Overall

The findings presented below are based on 23 studies with 3,786299 participants. Figure 5-1 demonstrates the forest plot and the summary effect using REM. Fourteen studies crossed the line of no effect (indicating no strong evidence that depression was associated with increased CHD risk). The pooled HR found a 22% increased risk of CHD in depressed patients (HR= 1.22, 95% CI, 1.13-1.32, $p < .000$) compared to patients without depression, with a substantial statistical heterogeneity ($I^2 = 77\%$, $p < .00001$). The observed statistical heterogeneity is most likely due to the clinical and methodological diversity of the Jee et al. (2019) cohort (see 5.5.1.2). None of the studies largely influenced this analysis, as each study weighed less than 10%.

Visual inspection of the funnel plot shows a degree of asymmetry, which may indicate the presence of publication bias (Figure 5-2). However, poor methodological quality could be a source of asymmetry as well (Higgins and Green, 2011). In the funnel plot, it is clear that the Gafarov et al. (2013) study, which is the smallest study in this meta-analysis, had a markedly different estimation compared to the other studies. This over-estimation of depression might reflect methodological shortcomings, such as inadequate accounting for confounders.

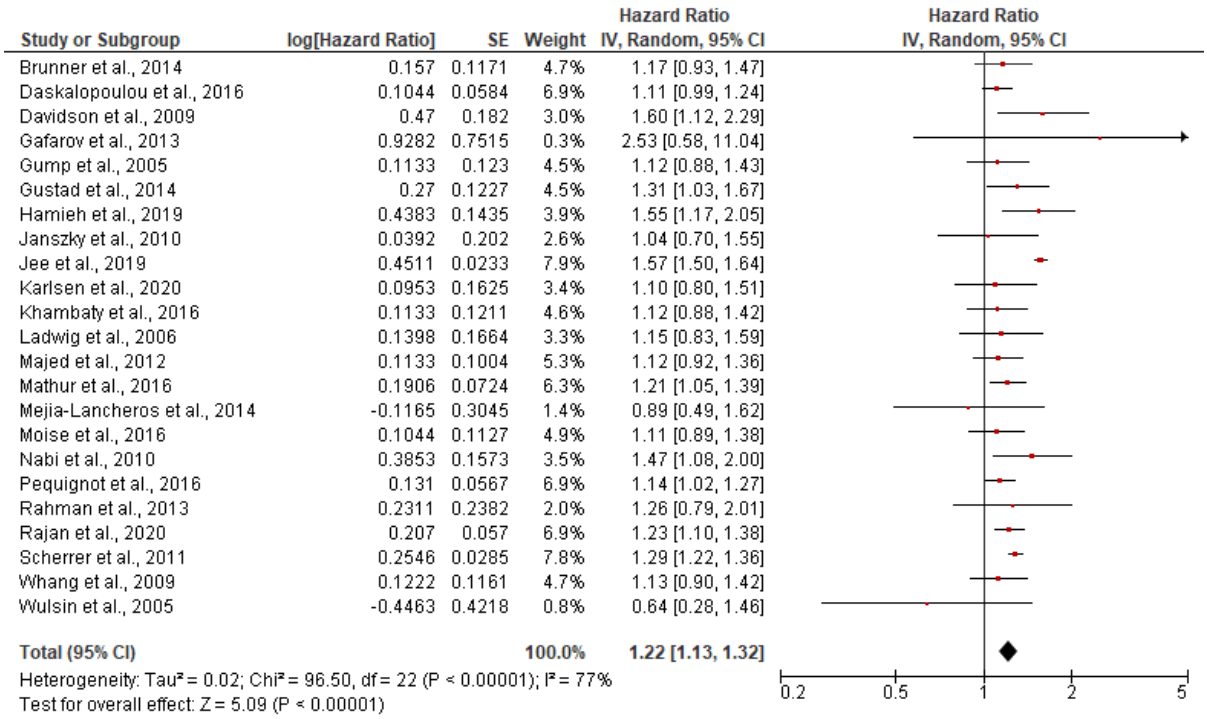

Figure 5-1 Forest plot showing the adjusted HR of CHD incidence for depressed participants compared with indivisuals with no depression, overall and in 22 CHD cohorts [RE model].
CI, confidence interval; IV, inverse variance; SE, standard error

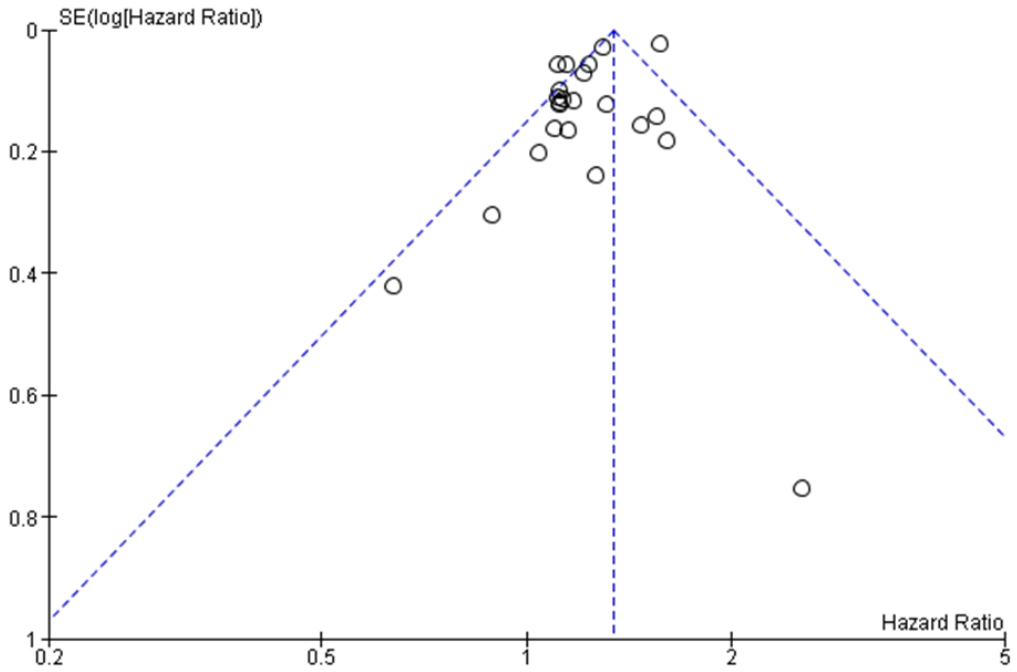

Figure 5-2 Funnel plot from 22 cohorts investigated the association between depressions and first-incidence of CHD. SE, standard error

5.5.1.2 **Sensitivity analysis**

Table 5-4 demonstrates the results for the one-study removed meta-analysis. Similar estimations of HRs were yielded across all meta-analyses, with HRs ranging from 1.21 to 1.23, suggesting that no single study affected the overall estimate. Nonetheless, sensitivity analyses excluding Jee et al. (2019) study resulted in a narrower 95% CI (HR = 1.21, 95% CI, 1.17, 1.26) and a marked reduction in I^2 statistics across studies, which was observed at 9%. These findings indicate that Jee et al. (2019) genuinely contributed to the whole statistical heterogeneity in my analysis.

Table 5-5 summarises all sensitivity analysis performed based on pre-specified criteria (see Section 5.4.2). Exclusion of studies that enrolled patients with a high risk of developing CVDs yielded an HR of 1.24 with a 95% CI between 1.14 and 1.34 and a *p*-value < .000 (Figure 5-4). Heterogeneity was substantial, as indicated by a chi-square test ($p < .000$) and I^2 statistics, which were observed at 79%. As shown in Figure 5-5, excluding studies that had used broad nonspecific criteria to identify depressed cases did not significantly affect the main result (HR = 1.23, 95% CI, 1.13, 1.33, $I^2 = 80\%$). Sensitivity analysis removing studies that did not control for potential confounders resulted in an HR of 1.22 and a 95% CI of 1.13-1.32, with substantial heterogeneity ($p < .00001$, $I^2 = 79\%$; Figure 5-6). Restricting the analysis to the five studies that had excluded CHD events occurring within the first years of follow-up yielded a similar estimated risk giving an HR of 1.22 with a marginally wider 95% CI ranging between 1.01 and 1.48. An important level of heterogeneity was observed ($p < .000$, $I^2 = 88\%$; Figure 5-7). Nabi et al. (2010a) reported a similar pattern of association (adjusted HR = 1.94, $p < .001$), though full data were not provided.

I also examined the effect of depression measured at multiple time points on the risk of CHD (Figure 5-8). Pooling HRs from the five studies that analysed depression as a time-dependent variable showed a slight reduction in the estimated risk compared to the primary analysis (HR = 1.17, 95% CI, 1.07, 1.28). The chi-square test for heterogeneity yielded a *p*-value of 0.36 and I^2 statistics were observed at 8%, indicating trivial heterogeneity. The combined estimates are likely to be driven by the Péquignot et al. (2016) cohort which carried about 50% of the total weight.

Figure 5-9 illustrates the findings after restricting the analysis to studies investigating the association between depression and CHD or stroke within the same population. This resulted in a similar estimate (HR = 1.22, 95% CI, 1.10, 1.35) with substantial statistical heterogeneity ($p < .000$, $I^2 = 86\%$).

Table 5-4 Depression and risk of CHD: Sensitivity analysis excluding studies in turn (leave-one-out approach)

Study	HR (95%CI)	P-value	I^2
Overall effect (REM)	**1.22 (1.13,1.32)**	**<0.000**	**77%**
(Brunner et al., 2014)	1.22 (1.13,1.33)	<0.000	78%
(Daskalopoulou et al., 2016)	1.23 (1.14,1.33)	<0.000	75%
(Davidson et al., 2009)	1.21 (1.12,1.31)	<0.000	78%
(Gafarov et al., 2013)	1.22 (1.13,1.32)	<0.000	78%
(Gump et al., 2005)	1.23 (1.13,1.33)	<0.000	78%
(Gustad et al., 2014a)	1.22 (1.12,1.32)	<0.000	78%
(Hamieh et al., 2019)	1.21 (1.12, 1.31)	<0.000	78%
(Janszky et al., 2010)	1.23 (1.13,1.33)	<0.000	78%
(Jee et al., 2019)	**1.21 (1.16,1.26)**	**0.34**	**9%**
(Karlsen et al., 2020)	1.23 (1.13,1.33)	<0.000	78%
(Khambaty et al., 2016)	1.23 (1.13,1.33)	<0.000	78%
(Ladwig et al., 2006b)	1.22 (1.13, 1.32)	<0.000	78%
(Majed et al., 2012)	1.23 (1.13,1.33)	<0.000	77%
(Mathur et al., 2016)	1.22 (1.13,1.32)	<0.000	78%
(Mejia-Lancheros et al., 2014)	1.23 (1.14,1.33)	<0.000	78%
(Moise et al., 2016)	1.23 (1.13, 1.33)	<0.000	78%
(Nabi et al., 2010a)	1.21 (1.12,1.31)	<0.000	78%
(Pequignot et al., 2013)	1.23 (1.13,1.33)	<0.000	76%
(Rahman et al., 2013)	1.22 (1.13,1.32)	<0.000	78%
(Rajan et al., 2020)	1.22 (1.12, 1.32)	<0.000	78%
(Scherrer et al., 2011)	1.21 (1.11, 1.33)	<0.000	78%
(Whang et al., 2009)	1.23 (1.13,1.33)	<0.000	78%
(Wulsin et al., 2005)	1.23 (1.14,1.33)	<0.000	78%

Abbreviations: CI, confidence interval; HR, hazard ratio; I^2, I-square test; REM, random-effect model.

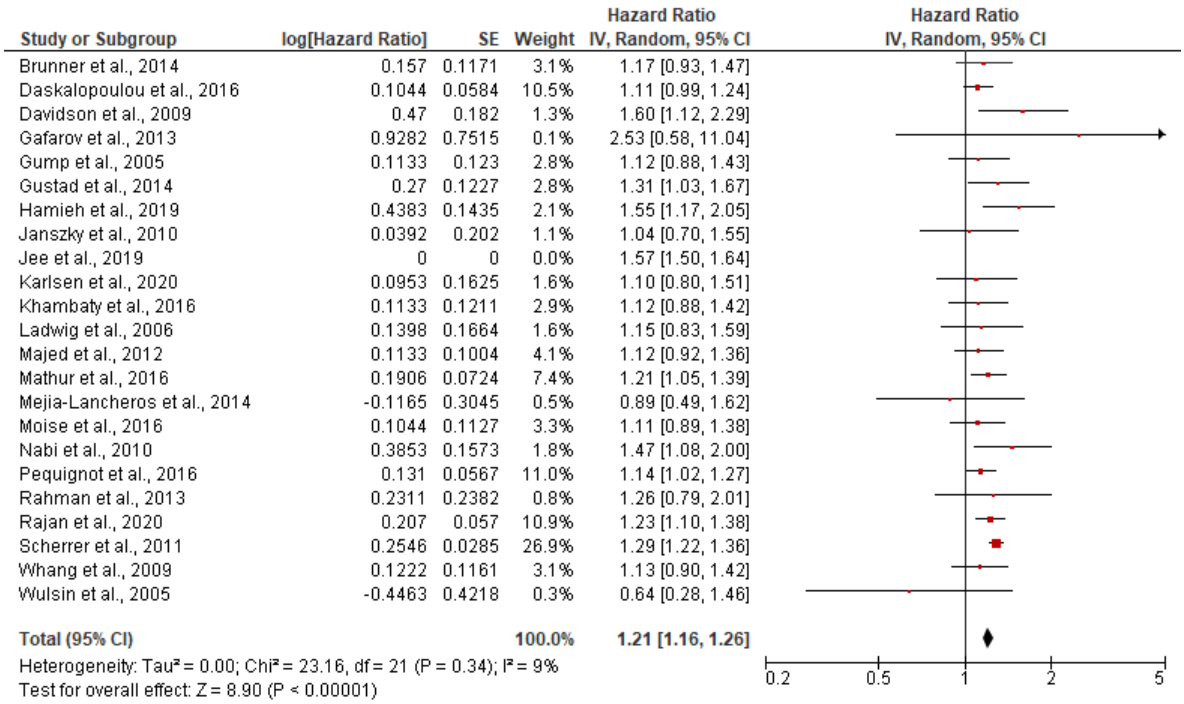

Figure 5-3 Forest plot showing the adjusted HR of CHD for depressed participants compared with indivisuals with no depression [Sensitivity analysis: Leave-one-out meta-analysis (excluding Jee et al. (2019)]

Table 5-5 Depression and risk of CHD: Sensitivity analysis summary

Sensitivity analysis		K	HR (95%CI)	*P*-value for heterogeneity	I^2
Overall effect	**RE model**	23	1.22 (1.13,1.32)	<0.000	77%
Excluding studies enrolling participants at high risk of CVD	(Khambaty et al., 2016, Gump et al., 2005, Mejia-Lancheros et al., 2014)	20	1.24 (1.14,1.34)	<0.000	79%
Excluding studies used unspecified diagnosis of depression	(Rahman et al., 2013, Brunner et al., 2014, Janszky et al., 2010)	20	1.23 (1.13,1.33)	<0.000	80%
Excluding studies not controlling for important covariates	(Brunner et al., 2014, Gafarov et al., 2013)	21	1.22 (1.13,1.32)	<0.000	79%
Studies excluding events occurred with 1st years	(Brunner et al., 2014, Gustad et al., 2014a, Jee et al., 2019, Majed et al., 2012, Rajan et al., 2020)	5	1.22 (1.01, 1.48)	<0.000	88%
Studies reported risk of time-varying depression	(Brunner et al., 2014, Hamieh et al., 2019, Moise et al., 2016, Péquignot et al., 2016, Whang et al., 2009)	5	1.17 (1.07, 1.28)	0.36	8%
Studies examined CHD and stroke outcomes simultaneously within the same population	(Brunner et al., 2014, Daskalopoulou et al., 2016, Gafarov et al., 2013, Gump et al., 2005, Jee et al., 2019, Karlsen et al., 2020, Majed et al., 2012, Mathur et al., 2016, Mejia-Lancheros et al., 2014, Moise et al., 2016, Nabi et al., 2010a, Péquignot et al., 2016, Rahman et al., 2013, Rajan et al., 2020)	14	1.22 (1.10,1.35)	<0.000	86%

Abbreviations: CI, confidence interval; HR, hazard ratio; $I^{2,}$ I-square test; MDD, major depressive disorders; K, number of studies; REM, random-effect model.

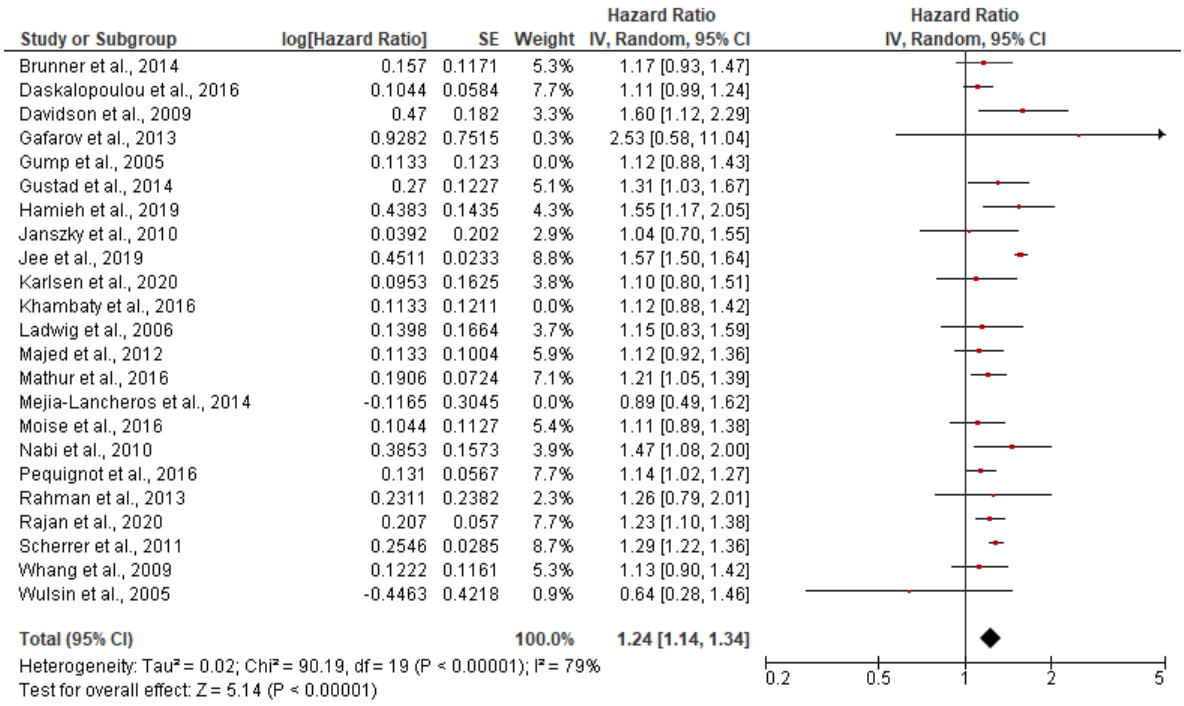

Figure 5-4 Forest plot showing the adjusted HR of CHD for depressed participants compared with indivisuals with no depression [Sensitivity analysis: Excluding studies enrolled participants at high risk of developing CVD]

CI, confidence interval; IV, inverse variance; SE, standard error

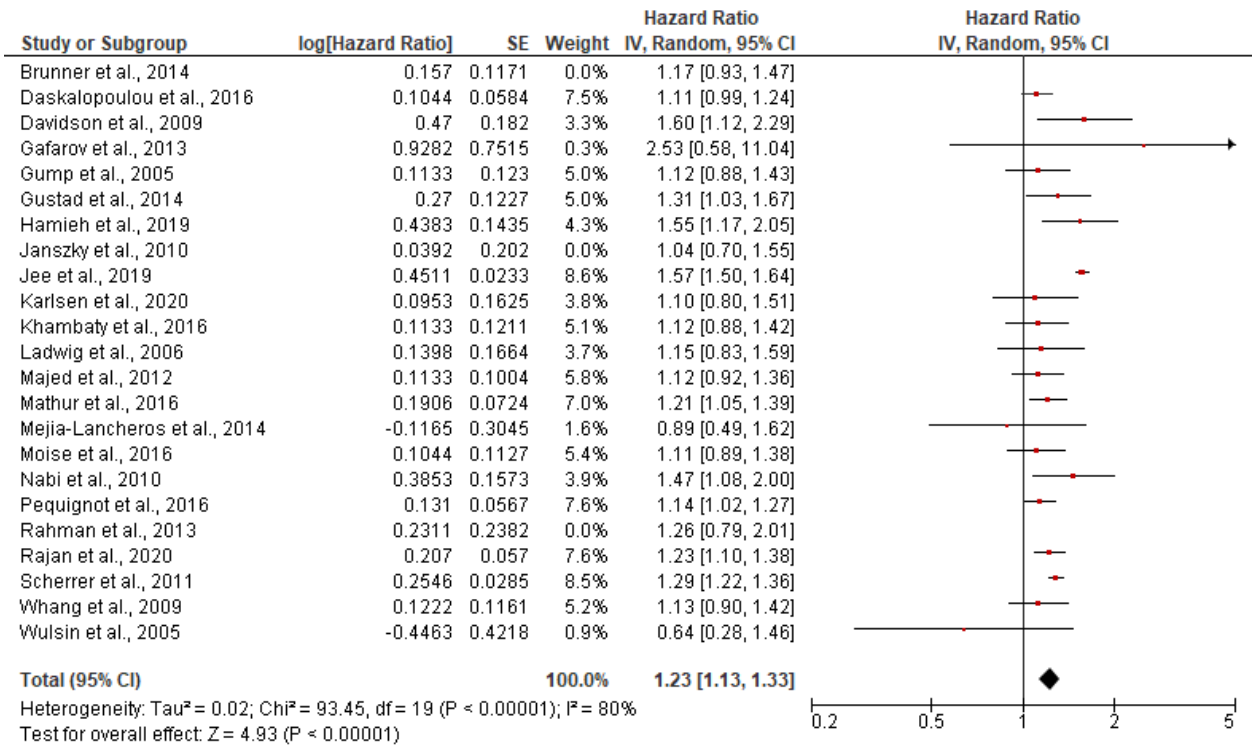

Figure 5-5 Forest plot showing the adjusted HR of CHD for depressed participants compared with indivisuals with no depression [Sensitivity analysis: Excluding studies used unspecified diagnostic or screening tools to identify cases of depression]
CI, confidence interval; IV, inverse variance; SE, standard error

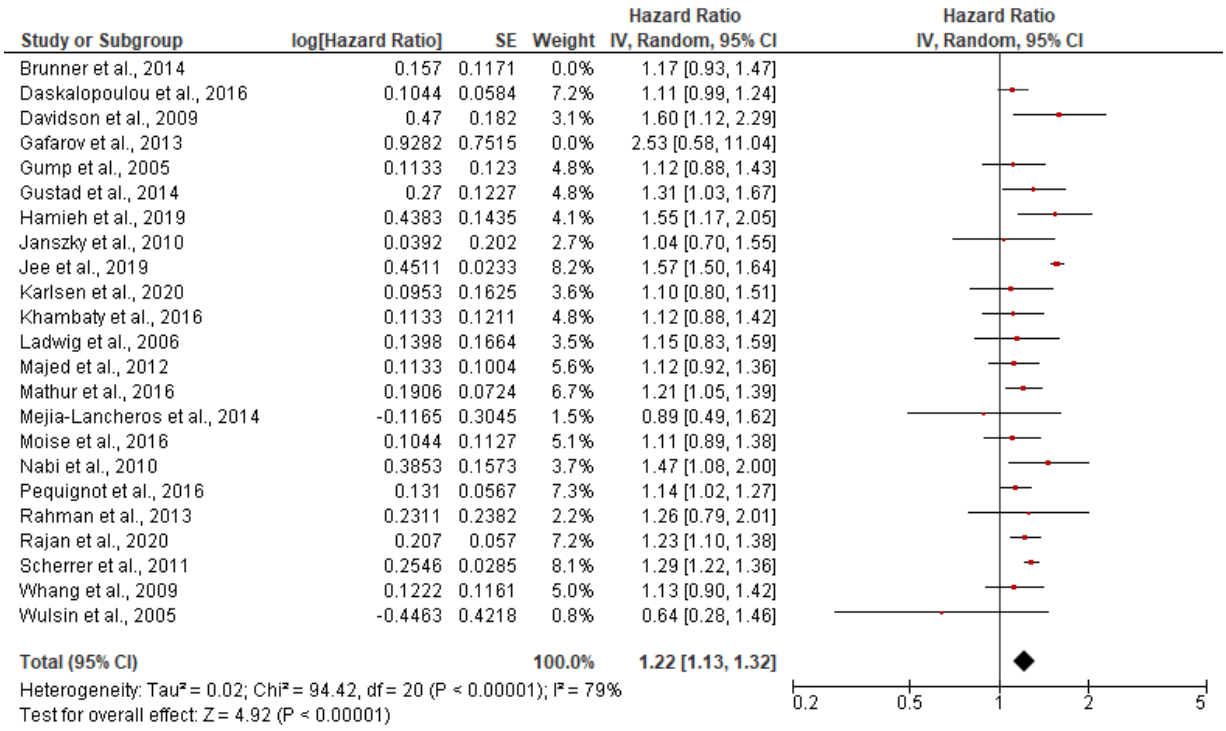

Figure 5-6 Forest plot showing the adjusted HR of CHD for depressed individuals compared with individuals with no depression [Sensitivity analysis: Excluding studies not adequately adjusted for potential confounders]

CI, confidence interval; IV, inverse variance; SE, standard error

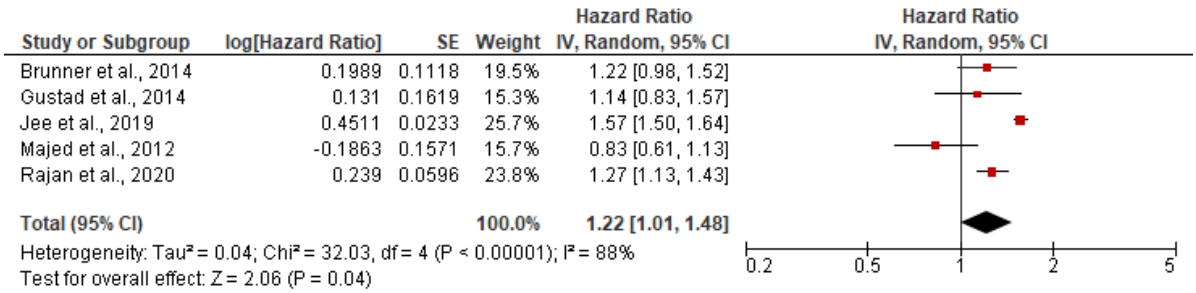

Figure 5-7 Forest plot showing the adjusted HR of CHD for depressed participants compared with indivisuals with no depression [Sensitivity analysis: studies excluded CHD incident occurred within the first years].
CI, confidence interval; IV, inverse variance; SE, standard error

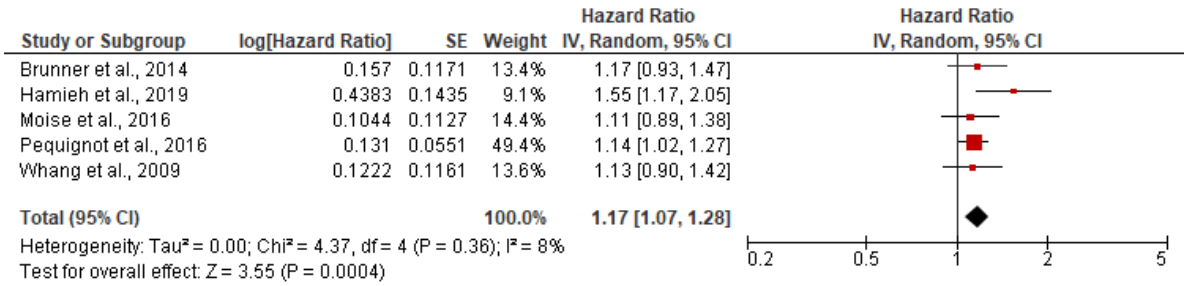

Figure 5-8 Forest plot showing the adjusted HR of CHD for depressed individuals compared with indivisuals with no depression [Sensitivity analysis: studies assessed depression as a time-dependent exposure]

CI, confidence interval; IV, inverse variance; SE, standard error

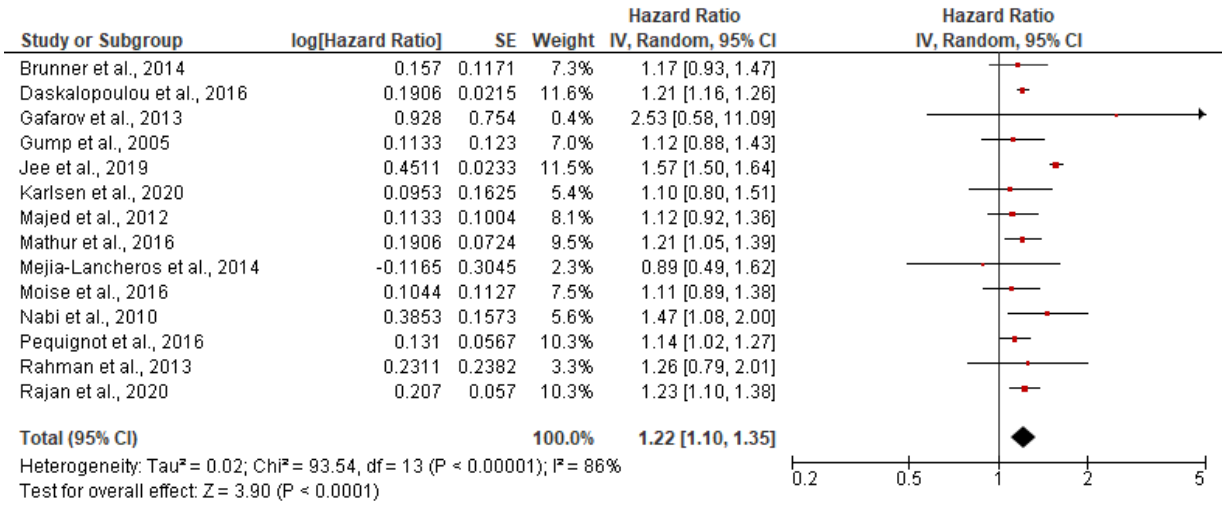

Figure 5-9 Forest plot showing the adjusted HR of CHD for depressed participants compared with indivisuals with no depression [Sensitivity analysis: Including cohorts that examined risk of developing stroke and CHD simultaneously as their primary outcomes and calculated the HRs for each outcome separately]

CI, confidence interval; IV, inverse variance; SE, standard error

5.5.2 Depression and risk of incident CHD: Subgroup analysis

Table 5-6 summarises the results for subgroup analyses examining the stability of the primary results and exploring factors that likely modify the association. Overall, eight subgroups explore the impact of depression on first-onset CHD, stratified according to the type of depression measure, duration of follow-up, mean age at baseline, CHD subtypes, type of gender, patient's CVD status at baseline, sample size and geographical location of study. Results from the primary overall analysis are included for reference.

5.5.2.1 By type of depression assessment

Figure 5-10 depicts the meta-analysis of depression by type of assessment method. Fourteen studies enrolling 23,1439 participants used a validated SRS tool for depression screening. The combined effect estimate resulted in an HR of 1.19, with 95% CI of 1.11-1.27 (p = .001). Statistical heterogeneity was trivial (p = .40, I^2 = 5%). The direction of this finding was affected mainly by Péquignot et al. (2016) study, which carried around 30% of the total weight. Seven studies identified depression via structured clinical diagnostic interviews or clinical diagnosis, with 1,136,145 patients combined. Pooling of effect estimates from these studies yielded an HR of 1.26 (95% CI, 1.20, 1.32, p < .0001). Assessment of heterogeneity showed a chi-square test p-value of 0.65 and I^2 statistics of 0%, indicating no statistical heterogeneity between studies. Scherrer et al. (2011) study greatly influenced the direction of this analysis, as it carried more than 67% of the assigned weight. Three studies enrolling 2,455,369 participants identified depression cases by clinical assessments combined with the use of antidepressant medications. The summary effect estimates resulted in an HR of 1.18 (95% CI, 0.86,1.63, p = .22) with evidence of substantial heterogeneity (p < .00001, I^2 = 95%). Finally, five studies with 994,306 participants determined the CHD risk associated with the use of antidepressants in additional analyses. Pooling the effect estimates showed an HR of 1.03 (0.63, 1.69, p = .91) with statistically considerable heterogeneity (p < .00001, I^2 = 98%). Weight was evenly distributed across the studies. Scherrer et al. (2011) study explained 54% of the total variation between studies, perhaps due to population heterogeneity (diabetic population).

No significant statistical difference was observed between studies (p = .47).

5.5.2.2 By duration of follow-up

A follow-up duration of 10 years, just below the average follow-up of the included studies, was set as a cut-off point for the group studies. Sixteen cohorts with 3,283,382 participants had been conducted over 10 years or longer. The pooled HR, as demonstrated in Figure 5-11, showed a 23% increase in CHD risk among depressed patients (HR 1.23, 95% CI, 1.11, 1.36, $p < .0001$). Assessment of heterogeneity found considerable statistical variation between studies ($p < .000$, $I^2 = 80\%$). Data for studies with a follow-up duration of less than 10 years were obtained from seven studies enrolling 502,917 participants. The pooled effect estimate resulted in an HR of 1.23 and a 95% CI between 1.11 and 1.35 ($p < .000$). Low heterogeneity was detected by a chi-square p-value of < .28 and I^2 statistics of 20%. The test for subgroup differences suggests no statistically significant group effect ($p = .97$).

5.5.2.3 By mean age groups

For studies with patients' mean age of less than 65 years, data were available from 3,768,588 participants enrolled in 19 cohorts (Figure 5-12). Combined effect estimates resulted in an HR of 1.24 with a 95% CI of 1.14-1.34 ($p < .000$). The chi-square test resulted in a p-value of <.000 and the I^2 statistics were observed at 75%, indicating considerable statistical heterogeneity. None of the individual studies had a large influence on this analysis. Data for studies with an older mean age (≥ 65 years) were available from 17,711 patients enrolled in three cohorts. Pooling effect estimates showed an HR of 1.13 with a 95% CI between 1.02 and 1.25 ($p = .02$). No statistical heterogeneity was observed between the studies ($p = 0.42$, $I^2 = 0\%$). The overall effect was strongly influenced by Péquignot et al. (2016) study which carried most of the assigned weight (86.5%). Testing for subgroup differences showed no statistically significant differences ($p = .15$).

5.5.2.4 By type of CHD endpoints

Figure 5-13 demonstrates the impact of depression on CHD stratified by type of CHD endpoints, including fatal/non-fatal MI, composite CHD and angina.

Results for MI were available from participants 3,651,404 enrolling in 12 studies with a pooled HR of 1.24 (95% CI, 1.19, 1.29, $p < .00001$). No statistical

heterogeneity was observed between studies (p = .48, I^2 = 0%). This analysis was greatly influenced by Scherrer et al. (2011) study, which carried almost half of the overall weight (49%). Data for a composite endpoint of fatal and non/fatal CHD were obtained from 12 studies enrolling 616,250 patients. Pooling effect estimates resulted in an HR of 1.29 with a 95% CI between 1.16 and 1.57 (p = .002). Evidence for substantial heterogeneity was detected (p < .000, I^2 = 78%). The two largest cohorts in this review provided data for risk of angina from 2,418,715 patients. An analysis of these results showed an HR of 1.57 (95% CI 1.40,75, p < .00001) with moderate to considerable heterogeneity (p = .08, I^2 = 68%). This analysis was mainly driven by Jee et al. (2019) study, which carried 60% of the total weight. Although the test for subgroup differences suggests that there is a statistically significant subgroup effect (p < .000), the number of studies in the angina subgroup (n = 2) was insufficient for an accurate comparison. Additionally, some of the studies' participants contributed to more than one of the subgroups in the forest plot (Daskalopoulou et al., 2016, Jee et al., 2019).

5.5.2.5 **By gender**

As shown in Figure 5-14, data were stratified based on gender. The first group comprised eight cohorts with 373,614 male participants. The pooled HR showed that depression increased the risk of incident CHD in men by 23% (HR 1.23, 95% CI, 1.06, 1.43, p = .007). Heterogeneity among these studies was substantial, as indicated by I^2 = 67% and a chi-square p-value of .003. The second group for women consisted of five cohorts with 285,462 individuals and the HR showed a stronger effect of depression for female participants (HR 1.50, 95% CI, 1.25, 1.81, p = .001) with modest heterogeneity (p = 0.23, I^2 = 29%). Jee et al. (2019) study carried the largest weight in both the male and female groups.

5.5.2.6 **By sample size**

Studies were stratified based on sample size into less than 10,000, between 10 and 100 thousand and those which have extremely large sample size more than 100,000 thousand (Figure 5-16). The magnitude of HRs were roughly around 20 and results from all subgroup analysis are in the same direction indicating increased risk of CHD in depressed individuals compared to non-depressed individuals.

5.5.2.7 **By study location**

Stratification of studies according to their geographical regions resulted in two subgroups (Figure 5-17). A data synthesis of HRs obtained from 13 European studies showed that depression was associated with a 17% increase in first-onset CHD (HR 1.17, 95% CI, 1.11, 1.24, p = .00001) with no evidence of heterogeneity (p = .57 and I^2 = 0%). This finding was primarily influenced by the Daskalopoulou et al. (2016) and Péquignot et al. (2016) cohorts because they carried 24.2% and 25.6% of the total assigned weight, respectively. Data from US studies were available from eight cohorts enrolling 478,007 patients. The pooled HR found that depression increased risk of first-onset CHD by 20% (HR 1.20, 95% CI, 1.10, 1.32, p = .002) with trivial heterogeneity (p = .22, I^2 = 26%). Scherrer et al. (2011) drove the magnitude and direction of the combined estimate because it carried 42.2% of the total assigned weight.

Table 5-6 Depression and risk of CHD: Subgroup analysis summary

Subgroup analysis		K	N	HR (95%CI)	Heterogeneity *P*-value	I^2	Between-group *P*-value
Overall effect	**REM**	**23**	**3,786299**	**1.22 (1.13,1.32)**	**<0.000**	**77%**	
Type of depression assessment	SRS	14	23,1439	1.19 (1.11,1.27)	0.40	5%	0.47
	Clinical diagnosis	7	1,136,145	1.26 (1.20,1.32)	0.65	0%	
	Combined clinical diagnosis and AD	3	2,455,369	1.18 (0.86,1.63)	<0.000	95%	
	AD	5	994,306	1.03 (0.63,1.69)	<0.000	98%	
Duration of follow-up	< 10 years	7	502,917	1.23 (1.11,1.35)	0.28	20%	0.97
	≥ 10 years	16	3,283,382	1.23 (1.11,1.36)	<0.000	80%	
Mean age	≥ 65 years	3	17,711	1.13 (1.02,1.25)	0.42	0%	0.15
	< 65 years	20	3,768588	1.24 (1.14,1.34)	<0.000	75%	
CHD subtypes	MI	12	3,651,404	1.24 (1.19,1.29)	0.48	0%	0.002
	Composite endpoint (CHD and MI)	12	616,250	1.29 (1.16,1.57)	<0.000	78%	
	Angina	2	2,418,715	1.57 (1.40,1.75)	0.08	68%	
Type of gender	Male	8	373,614	1.23 (1.06,1.43)	0.003	67%	0.1
	Female	5	298,191	1.50 (1.25,1.81)	0.23	29%	
CVD status at baseline	Free of CHD and stroke	11	737,287	1.18 (1.11,1.25)	0.85	0%	0.41
	Free of CVD	13	3,071678	1.24 (1.11,1.38)	<0.000	83%	
Sample size	≥ 10,000 <100,000	10	253,329	1.20 (1.11,1.31)	<0.000	0%	0.39
	< 10,000	8	39,539	1.15 (1.05,1.25)	0.41	3%	
	≥100,000	5	3435478	1.28 (1.12,1.47)	0.0003	93%	
Study location	EU	13	2,681075	1.17 (1.11,1.24)	0.57	0%	0.66
	US, Canada	8	478,007	1.20 (1.10,1.32)	0.22	26%	
	Asia	1	481,355	1.57 (1.50,1.64)	NA	NA	
	Multinational	1	145,862	1.23 (1.10,1.38)	Na	NA	

Abbreviations: AD, antidepressants; CI, confidence interval; CHD; coronary heart disease; CVD, cardiovascular disease; EU, Europe; HR, hazard ratio; K, number of studies; MI, myocardial infarction; N, number of participants; REM, random-effect model; SRS, self-reported scale; US, United states.

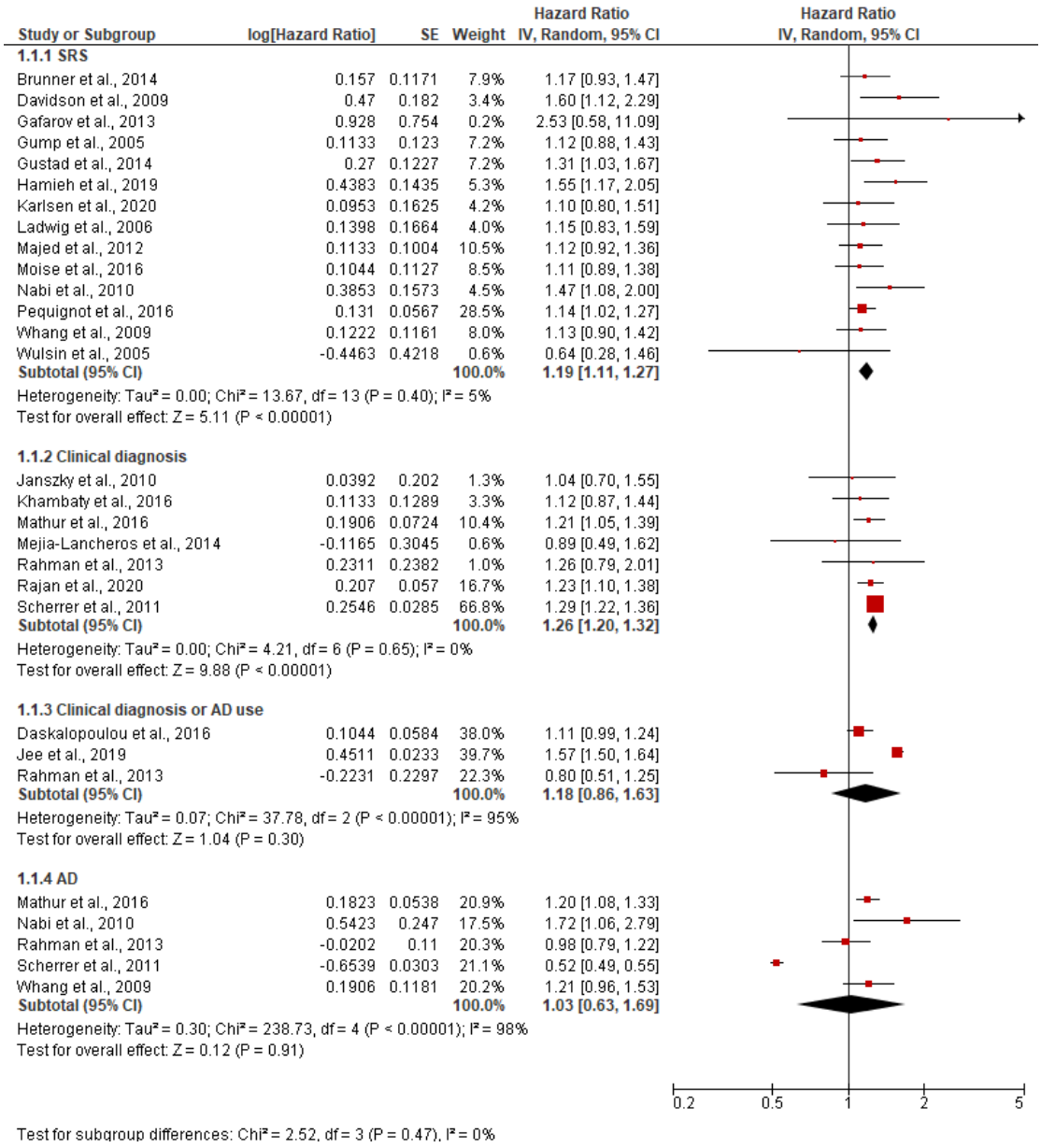

Figure 5-10 Forest plot showing the adjusted HR of CHD incidence for depressed individuals compared with indivisuals with no depression by type of depression assessment
Abbreviations: AD, antidepressants medication; CHD, coronary heart diseases; SE, standard error; SRS, self-reported scale.

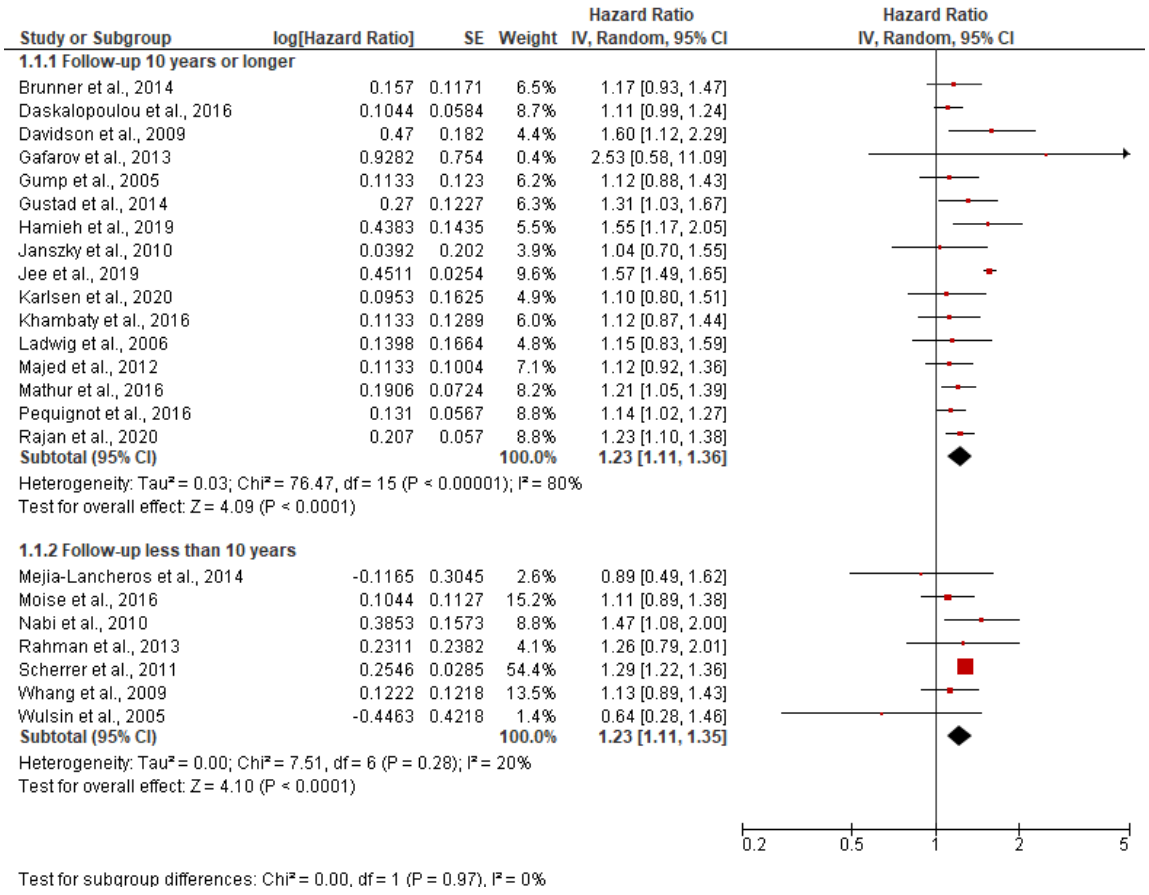

Figure 5-11 Forest plot showing the adjusted HR of CHD incidence for depressed individuals compared with indivisuals with no depression by duration of follow-up
Abbreviations: CHD, coronary heart diseases; SE, standard error.

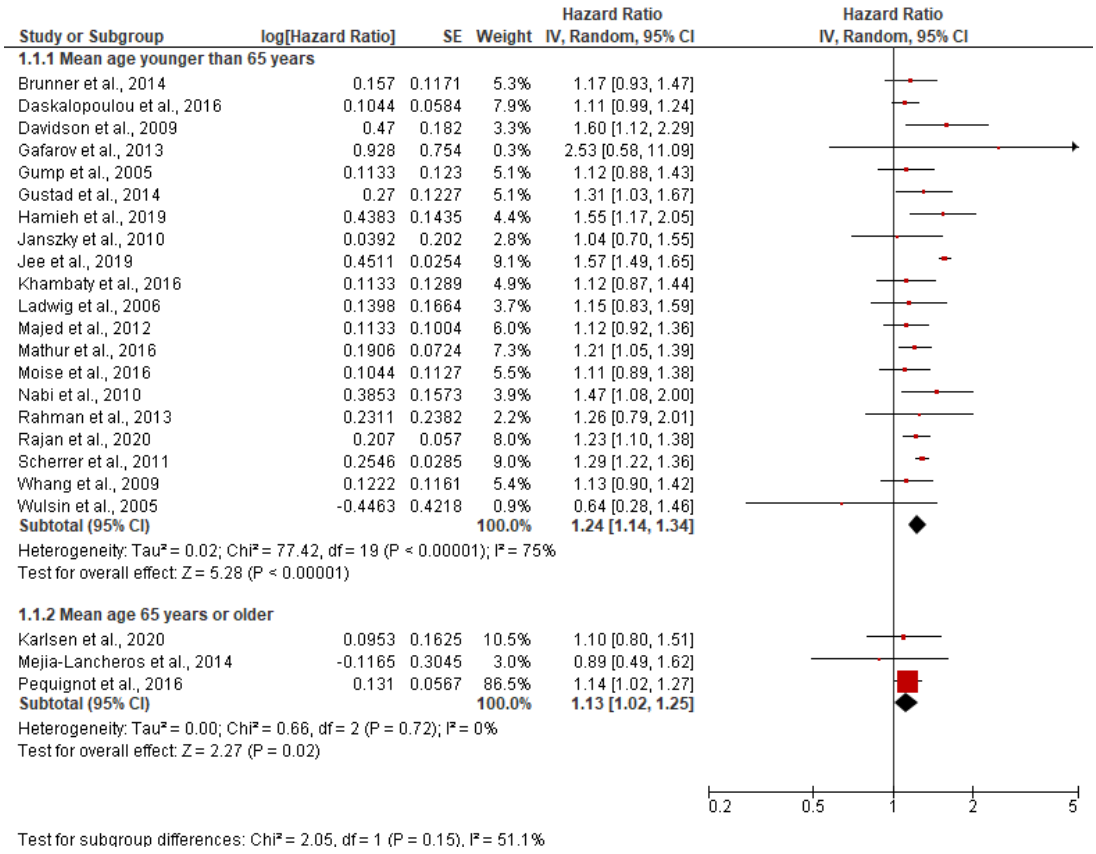

Figure 5-12 Forest plot showing the adjusted HR of CHD incidence for depressed individuals compared with indivisuals with no depression by study population's mean age
Abbreviations: CHD, coronary heart diseases; SE, standard error

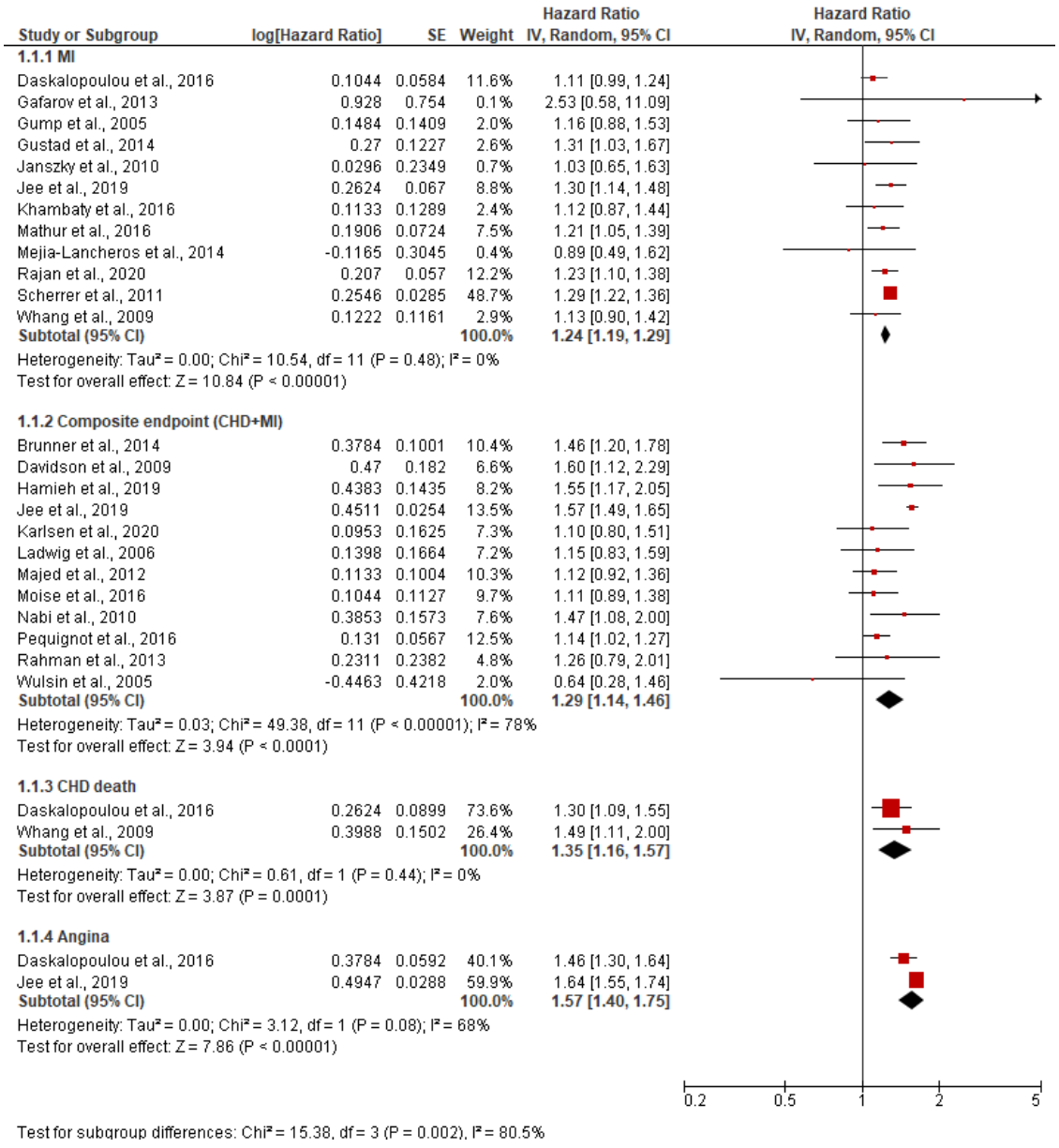

Figure 5-13 Forest plot showing the adjusted HR of CHD incidence for depressed individuals compared with indivisuals with no depression by CHD outcomes
Abbreviations: CI, confidence interval; CHD, coronary heart diseases; MI. myocardial infarction; SE, standard error

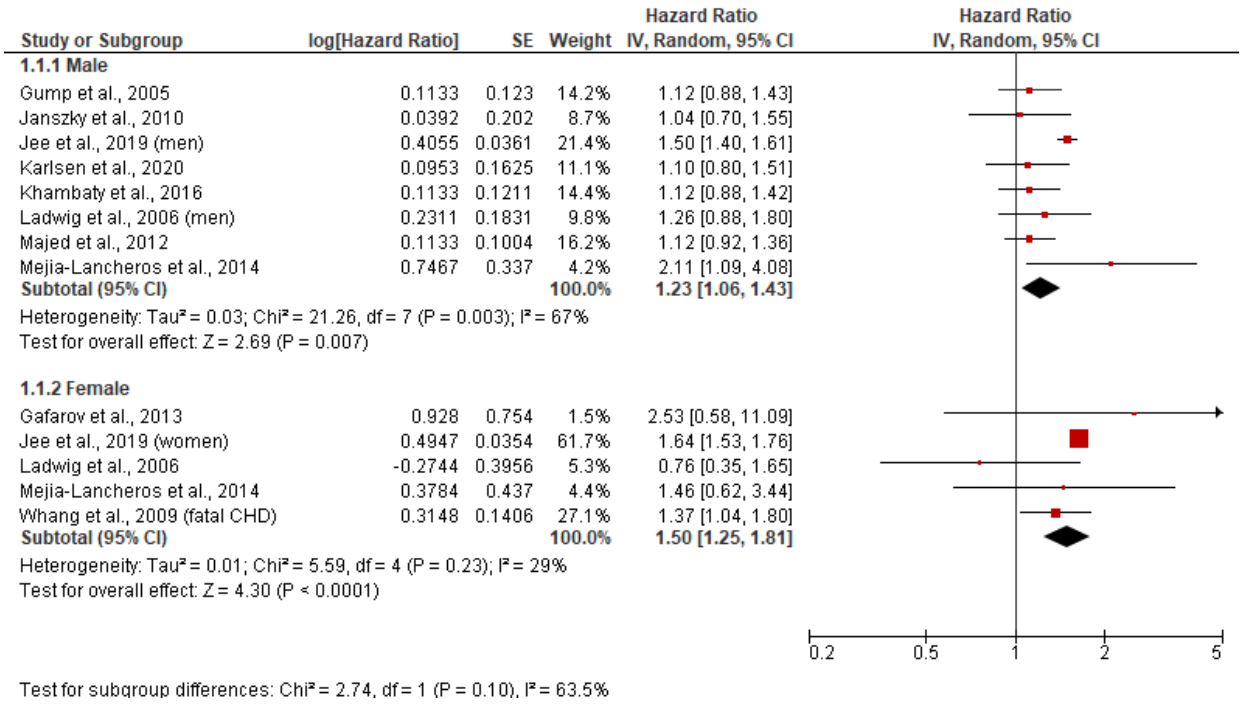

Figure 5-14 Forest plot showing the adjusted HR of CHD incidence for depressed individuals compared with individuals with no depression by gender
Abbreviations: CI, confidence interval; CHD, coronary heart diseases; SE, standard error

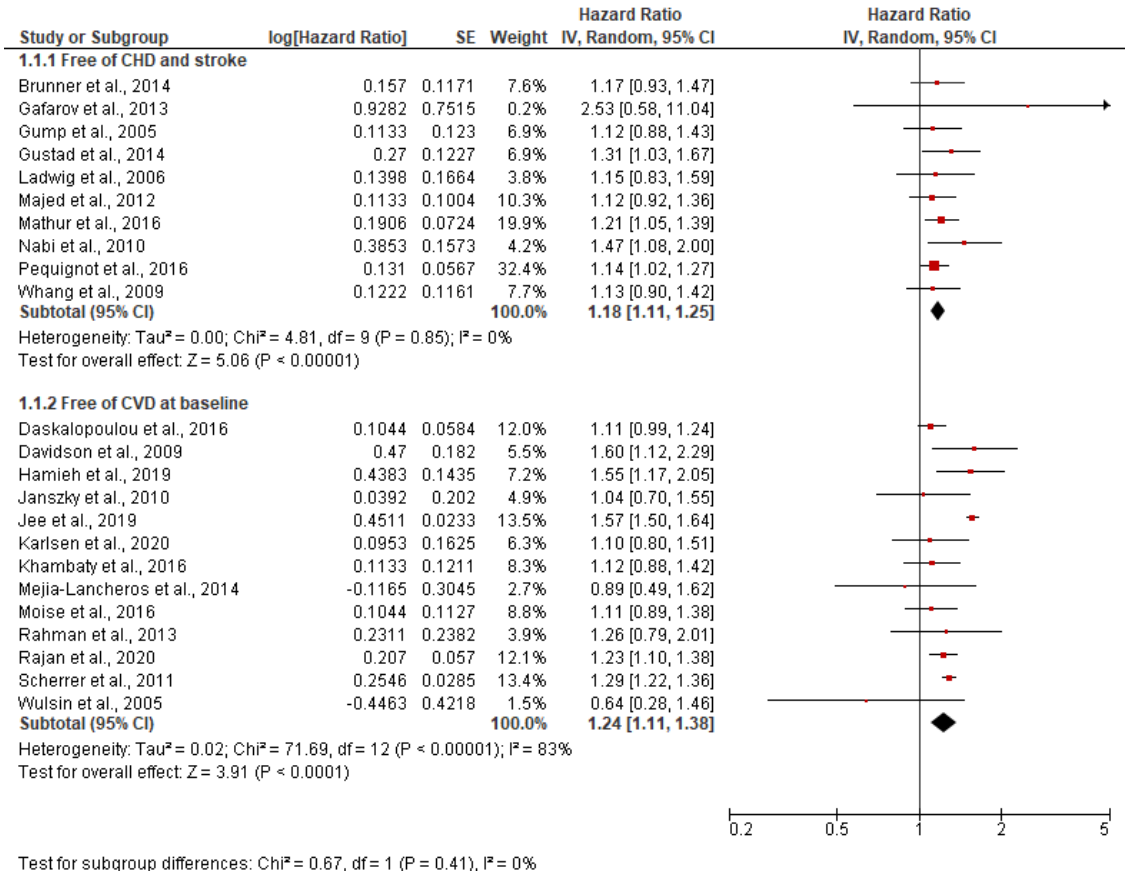

Figure 5-15 Forest plot showing the adjusted HR of CHD incidence for depressed individuals compared with indivisuals with no depression by type of population

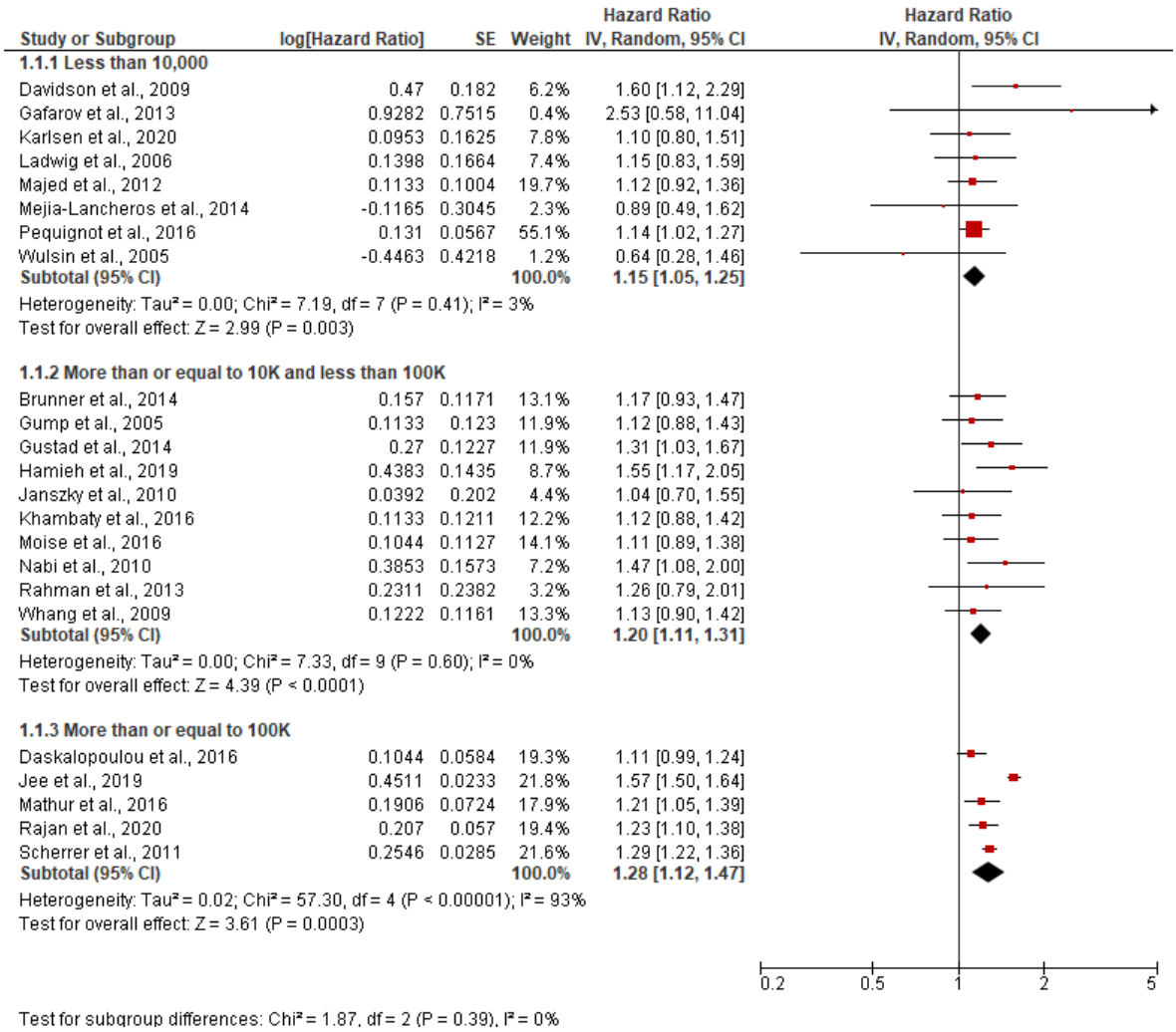

Figure 5-16 Forest plot showing the adjusted HR of CHD incidence for depressed individuals compared with indivisuals with no depression by study sample size
CI, confidence interval; IV, inverse variance; SE, standard error

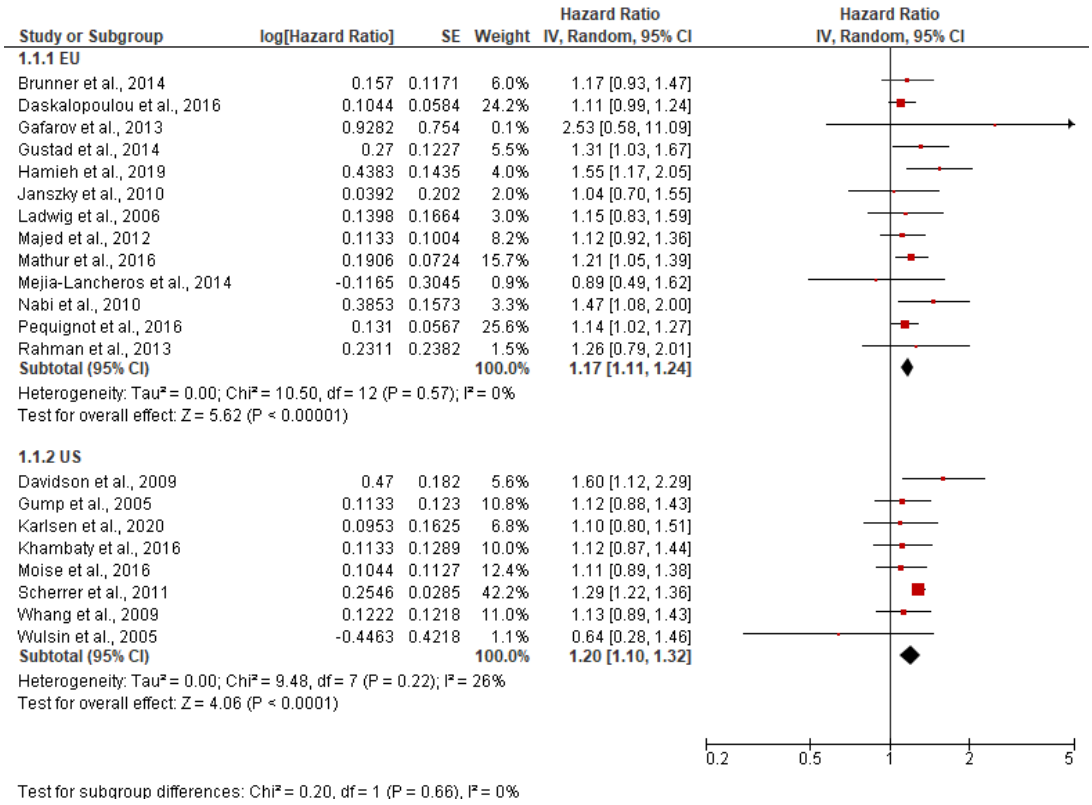

Figure 5-17 Forest plot showing the adjusted HR of CHD incidence for depressed individuals compared with indivisuals with no depression by location

Abbreviations: CI, confidence interval; CHD, coronary heart diseases; EU, Europe; SE, standard error; US, United States

5.6 Discussion

I sought to assess the relationship between depression and risk of CHD incident in patients with no known history of CHD or stroke prior to study entry. The primary analysis of the 23 studies using REM showed that participants with depression who were apparently free from stroke and cardiac diseases experienced a 22% increased risk of first-onset CHD events compared to non-depressed participants (HR = 1.22, 95% CI, 1.13, 1.32). My finding is in line with the latest systematic review and meta-analysis on this subject conducted by Wu and Kling (2016), who reported a 22% increased risk of CHD incident. A positive association was also found when analyses were performed for MI and angina: the corresponding estimated risks were 24% and 57%. The risk estimates yielded from the primary analysis, as well as the direction of the association, remained fairly stable when multiple exclusion criteria were applied within sensitivity analyses. There was, however, substantial variation between studies (I^2 = 77%, p < .000). Most of the variability between the studies observed in the primary analysis, in the subgroups and sensitivity analyses can be explained by the Jee et al. (2019) study. Exclusion of this cohort based on a leave-out meta-analysis approach resulted in a narrower 95% CI, an improvement on the overlaps between CI and a drastic decrease in the statistical heterogeneity (p = .44, I^2 = 9%). Because the magnitude of the estimated risk did not change (HR = 1.21, 95% CI, 1.16, 1.26), the large heterogeneity in this review should not be a concern. The pooled effect estimates of HR for incident CHD obtained from the 14 cohorts that measured CHD and stroke outcome simultaneously within the same population yielded a very close estimate effect (HR = 1.22, 95% CI, 1.10, 1.35, I^2 = 86%).

5.6.1 Dose response relationship

In this review, I evaluate the dose–response hypothesis in relation to depressive disorder and its prospective association with CHD incidence. Of eight cohorts that examined the dose response relation (Brown et al., 2011, Brunner et al., 2014, Gump et al., 2005, Gustad et al., 2014a, Jee et al., 2019, Nabi et al., 2010a, Whang et al., 2009, Wulsin et al., 2005), four had previously discussed it in relation to stroke outcomes. There were considerable methodological diversities in terms of how studies measured the dose-response effect of depression, as discussed in section 4.5.1. Thus, generating a meta-analysis for those studies was not possible.

In the following section, I describe and discuss their results narratively. Of the eight cohorts, five investigated the relationship between the severity of depressive symptoms and the risk of developing CHD. Gump et al. (2005) divided the CES-D scores into quintiles and showed no statistically significant association between increasing the severity of depressive symptoms and risk of incident CHD. As described previously (See section 3.3.1), this study used uncommon cut-off scores (13) presenting the association for minor depressive symptoms (i.e. below a score of 13) and did not provide detailed data about the nature of the association beyond that point. Brown et al. (2011) applied the same screening tool and divided the CES-D scores into the following <16, 16–23 and ≥ 24. Their findings demonstrated a dose-response relationship between the CES-D score and CHD incidence. Compared to participants with a CES-D score < 16, participants with CES-D score ≥ 24 (RR = 1.61, 95% CI, 1.22, 2.11) and those with a CES-D score between 16–23 (RR = 1.36, 95% CI, 1.06, 1.74) had a higher RR of CHD risk. Wulsin et al. (2005) also used the CES-D screening tool and statistically derived three levels of severity based on gender-specific tertiles. The highest tertile of depressive symptoms was equivalent to scores above 9 for men and above 11 for women on the CES-D-scale. Their results showed no association between different levels of depressive severity and CHD risk for either gender (*p* for trend = .23), although it was likely underpowered to detect an association. Again, the dose-response relationship in this study was not tested in relation to different severity levels of clinically relevant depressive symptoms. Nabi et al. (2010a) used the BDI scale divided into nil (0-9), mild (10-18), moderate (19-29) and severe symptoms (30-36) and found a dose-response association with CHD, but it was not statistically significant. They further examined the association between continuous BDI scores and risk of CHD and showed that a one-unit increase in the BDI score is associated with an excess CHD risk of 3% (HR = 1.03, 95% CI, 1.02–1.05). Whang et al. (2009) utilised the MHI-5 screening tool and divided the participants into four categories of depressive symptoms according to their MHI-5 score (77–100, 76–85, 53–75, 0–52). The findings from their study demonstrated a dose-response relation with fatal CHD (*p*=0.007) but not with MI (*p*-value for trend = .19).

The other three cohorts examined the association between depression chronicity and risk of CHD. Two proposed a dose-response relationship between the

increasing number of depressive episodes experienced over the follow-up period and the risk of developing CHD (Brunner et al., 2014, Péquignot et al., 2016). Brunner et al. (2014) showed that compared to participants with no depressive symptoms, patients who experienced depressive symptoms 1-2 times during their lifetime were at a 12% increased risk of developing CHD, though with no statistical significance (HR = 1.12, 95% CI, 0.7–1.7), while those who experienced depressive symptoms 3 to 4 times had a twofold increased risk of developing CHD (HR = 2.06, 95% CI, 1.2–3.7, *p*-value for trend = .01). As previously mentioned, results from Brunner et al. (2014) were presented without adjusting for CVD risk factors. In the Péquignot et al. (2016) cohort, the risk for future CHD was evident with transient and cumulative depressive episodes – a finding that is similar to stroke outcomes. In Jee et al. (2019) study, the risk of depression over 10 visits, irrespective of gender, did not show a dose-response relationship, although each visit due to depression was significantly associated with incident CHD.

While these cohorts do not agree on a linear association between depression and CHD incidence, they all indicate that chronic depressive symptoms are associated with an increased risk of incident CHD. These findings contrast with one of the early studies that evaluated the effect of depression measured at multiple occasions on the risk of a new CVD event among elderly patients who were free of CHD (Penninx et al., 1998). The study found that chronic depression was not associated with an increased risk of incident CVD and concluded that chronic depression may not be a risk factor for CVD. The findings from these recent studies provide evidence that repeated exposure to depressive symptoms or chronic depression can indeed be a risk factor for CHD. Nonetheless, it should be noted that experiencing multiple depressive episodes over a period of time, however, predominantly reflects several depression subtypes (i.e. recurrent or persistent depression). There is a possibility that patients who have experienced recurrent depression may have a different genetic profile compared to those with single episodes. Studies suggest that recurrent depression reflects an underlying vulnerability that is largely based on genetic loading (Burcusa and Iacono, 2007, Shadrina et al., 2018). Further, it is well documented that depression and cardiac diseases share a common genetic background (Kendler et al., 2009, McCaffery et al., 2006, Scherrer et al., 2003). Thus, the significant association between depression and incident CHD in patients who experienced multiple depressive

episodes could be confounded by their distinct genetic variability and perhaps a unique disease profile. Consequently, the higher associated risk may mirror genetic predisposition rather than depression per se.

5.6.2 Depression as a time-varying exposure

I also evaluated the risk of future CHD associated with depression assessed at multiple instants over the course of follow-up. A sensitivity analysis of five studies examined the cumulative effect of depressive symptoms for a minimum of three measures over an average follow-up of 12.7 years. The findings showed that the risk of time-varying depression was relatively stable (HR = 1.17, 95% CI, 1.07, 1.28). Despite that no evidence of statistical heterogeneity being detected (p = .36, I^2 = 8%), the result from this analysis should be considered with caution due to the small number of studies that were incorporated to pool the risk estimate. However, it has been suggested that, in REM, the minimum number required is five studies to reasonably achieve power to detect an effect of interest (Jackson and Turner, 2017).

5.6.3 Reverse causality

One of the largest challenges that has been identified when studying the prospective association between depression and CHD is that both conditions are caused by subclinical manifestations of atherosclerosis (Carney and Freedland, 2003, Charlson and Peterson, 2002). Thus, a positive association between depression and subsequent CHD may reflect a reverse causation (i.e. subclinical manifestation of CVD causing depression). In a meta-analysis, Nicholson et al. (2006) found that the impact of depression on CHD incidence was more pronounced in studies with relatively short follow-up durations compared to those with longer follow-up durations and suggested a possibility of reverse causality. Similarly, in a subgroup analysis, Gan et al. (2014) presented that depression increased the risk of CHD in the group with less than 15 years of follow-ups (RR = 1.36, 95% CI, 1.24, 1.49), but no statistical significant association was found for the group with follow-ups equal to or more than 15 years (RR = 1.09, 95% CI, 0.96, 1.23). However, there are some concerns about the reliability of these results. As previously mentioned, the review conducted by Nicholson et al. (2006).contains early observational literature that controlled poorly for potential confounders,

which may explain the profound effect in some of their findings. In Gan et al. (2014) cohort, it appeared that the subgroup analysis by the follow-up duration suffers from uneven covariate distribution as there was a large imbalance in the number of studies within the subgroup (30 vs 5 studies). In addition, some study participants contributed to both subgroups, limiting a proper examination and interpretation for a possible subgroup difference (Richardson et al., 2019). I performed a subgroup analysis dividing my eligible studies into a group with a follow-up duration of less than 10 years and to a follow-up duration of 10 years or longer. In contrast to the past reviews, the results from my subgroup analysis showed no significant impact of the follow-up duration on the estimated risk. I found that depression is associated with a 23% (HR = 1.23, 95 CI%, 1.11, 1.35) and 21% (HR = 1.29, 95% CI, 1.14, 1.47) increased risk of CHD incident corresponding to studies with a follow-up duration of less than 10 years and those with 10 years or longer. These findings align with the results of Wu and Kling (2016) who found that depression significantly increases the risk of MI and CHD death based on studies that had a mean follow-up of eight years or longer. Although my review includes participants with no known history of CHD or stroke, the impact of reverse causality cannot be ruled out given that none of the included studies had measured the baseline level of subclinical atherosclerosis.

Subclinical atherosclerosis, the pathological mechanism underlying CHD, is known to take decades to manifest as clinical symptoms (Janszky et al., 2010). In this review, the average follow-up was about 12 years, and most of the included studies enrolled middle-aged or older participants who may already have had atherosclerosis before study entry. On balance, atherosclerosis could also be a pathological consequence of depression (Khan et al., 2020). To minimise the possibility of reverse causality, I pooled the summary effect from five studies that considered a lag period with the exclusion of incident CHD in the first years of follow-up. The pooled HR was comparable to the primary meta-analysis showing that depression is associated with a 22% (1.22, 95% CI, 1.01, 1.48) increased risk of CHD incident, which may reassure that the main findings in this review are not biased by reverse causality. However, the wide 95% CI and the substantial heterogeneity (p <.000, I^2 = 88%) limit drawing a firm conclusion.

5.6.4 **Types of depression assessment tools and CHD**

An evaluation of the different depression measurement types in a subgroup analysis showed that clinical depression had a stronger effect on incident CHD (HR = 1.26, 95% CI, 1.20, 1.32, I^2 = 0%) relative to depressive symptoms (HR = 1.19, 95% CI, 1.11, 1.27, I^2 = 5%), although no statistically significant difference between the groups exists (p = .47). This finding suggests that depressive symptoms do not need to reach a clinical/diagnostic threshold to be associated with CHD risk, corroborating my findings regarding stroke in the previous chapters as well as reports from the past reviews (Rugulies, 2002, Nicholson et al., 2006), which fit well with a dose-response hypothesis. By contrast, Gan et al. (2014) found that the association was much stronger in studies that identified depression using SRS rather than structured clinical diagnostic interviews or clinical diagnosis. Nevertheless, the subgroup analysis in this review was incapable of producing valid results, partly due to the imbalanced number of studies across their subgroups (29 studies vs 4 studies). Conversely, depressed patients identified through a clinical assessment and or usage of antidepressants yielded a null association. This result is contrary to those obtained from stroke analysis, which showed that depressed cases identified by clinical diagnosis and/or anti-depressants are associated with increased risk of stroke.

In the last subgroup, I evaluated the independent effect of antidepressants on incident CHD and found no evidence that antidepressants were associated with an increased risk of developing CHD (p = .91).

Overall, meta-analysis studies examining the effect of antidepressant use and risk of incident CHD among healthy individuals are limited. My finding is comparable with one of the few meta-analyses of observational studies enrolling participants with no history of CHD (Oh et al., 2014). This review of 7 case–control and 11 cohort studies found that neither SSRIs nor TCAs were associated with an increased risk of a first-onset CHD event. More recently, a prospective cohort study of 238,963 patients aged 20 to 64 years with a first diagnosis of depression and free of previous MI found no evidence of an association between antidepressant class and risk of MI over five years of follow-up (Coupland et al., 2016). The effect of antidepressants on CHD incidence was not studied in previous meta-analyses that examined the association between depression and CHD (Gan et al., 2014,

Nicholson et al., 2006, Rugulies, 2002, Wu and Kling, 2016, Wulsin and Singal, 2003). My findings provide separate risk estimations which help to recognise the potentially distinct effect of depression and antidepressant use on incident CHD in individuals with no known history of CHD or stroke. The result from my subgroup analysis should be considered with caution due to the significant amount of heterogeneity between studies (I^2 = 98%). Additionally, my result is limited by inadequate drug information on the type of antidepressants, dosage regimen and adherence. These findings clearly show how results may alter based on different diagnostic criteria used to identify depression, which could interfere with correct identification of CVD risk association or result in improper patient care plans. Altogether this evidence further supports my conclusion in previous chapter that current clinical practice lack evidence about the optimal methods for assessing depression and future studies should examine different diagnostic criteria and establish the possible optimal one.

5.6.5 **Risk by type of CHD endpoint**

Two studies provided further information on angina pectoris as a CHD outcome (Daskalopoulou et al., 2016, Jee et al., 2019). The magnitude of the estimated risk provided by each study was much more profound compared to the risk estimates for other CHD endpoints within the same studies. The pooled HR showed that depression increased the risk of developing angina by 57% (HR = 1.57, 95% CI, 1.40, 1.75, I^2 = 68%). However, note that both cohorts that were used to pool the risk estimate identified the depressive cases by antidepressant usage in addition to clinical diagnosis (which are both subject to potential misclassification) and perhaps the potential bias of doing led to an overestimation of effect size. Another explanation for the larger effect observed in this subgroup is that the effect size obtained from the primary meta-analysis was based on studies that had mostly (80%) relied on hard primary endpoints (CHD death and MI), which are more likely to be less susceptible to manipulation or bias as soft endpoints (angina). Research has shown that an angina diagnosis is problematic as people with depression or other mood disorders are more likely than others to report angina-like chest pain in the absence of any narrowed coronary artery (Carter et al., 1997, Lantinga et al., 1988, Serlie et al., 1995, Kim et al., 2017b). Although results form this subgroup is limited due to the very small number of included studies, , it would

be expected that studies restricting their outcomes to hard endpoints as a conservative approach would underestimate the effect of depression on CHD.

My subgroup analysis for MI outcome showed that depressed patients were at a 24% higher risk of developing MI compared to non-depressed patients (HR = 1.24, 95% CI, 1.19, 1.29, I^2 = 0%). In the Wu and Kling (2016) review, only studies with a hard endpoint, including MI and fatal CHD, were eligible. The reviewers synthesised data from eight studies and reported that depression is associated with a 30% increased risk of MI. My subgroup result for MI outcome is highly consistent with those obtained from the primary analysis of the current study for all CHD events, including definite angina, leading to the conclusion that the result reported herein is not driven by 'soft' endpoints.

5.6.6 **Gender differences**

Generally, men are known to have a higher propensity for developing CHD than women (Bots et al., 2017). Epidemiological studies have suggested that premenopausal women are at lower risk of developing CVD compared to age-matched men. The reduced risk is attributed at least partly to oestrogen, which have been suggest to have protective mechanism against CVD (Iorga et al., 2017).However, women are twice as likely as men to develop depression during their lifetime (Kuehner, 2017). Therefore, does that mean that depression increases the risk among women to develop CHD compared to men? Several studies suggest that gender, particularly younger women, could be a predictor of poor prognosis in patients with established CHD (Greenland et al., 1991, Vaccarino et al., 1998), which may partly explain why women with depression face higher mortality rates after a CHD event compared to men with depression (Mallik et al., 2006). In this review, I examined whether depressed females compared to depressed males were at a higher risk of developing CHD by conducting a subgroup analysis. The results showed that depression significantly increased the risk of CHD in women by 50% (HR = 1.50, 95% CI, 1.25, 1.81, I^2 = 29%) compared to 23% in men (HR = 1.23, 95% CI, 1.06, 1.43, I^2 = 67%), but no significant between-group differences were observed (p = .1). My finding that depressed women experienced a higher risk of CHD is not completely congruent with previous meta-analyses. Wu and Kling (2016) found that depression increased the risk of CHD in men but not in women. Similarly, Gan et al. (2014) found that the depression effect on CHD

was more evident in men. Nonetheless, the risk estimations provided by both meta-analyses were inaccurate, as male proportions were between 30%-40% in more than 70% of the studies used to detect gender-based differences. My result also differs from that of a recent meta-analysis conducted by Smaardijk et al. (2019).In a systematic review, Smaardijk et al. (2019) assessed the association between different psychological factors, including depression and the development of CHD stratified by gender. The authors showed that the associations of depression with CHD did not differ between women and men (Smaardijk et al., 2019). They identified 34 studies provided data for men and, after pooling the risk estimate, they found that depression is associated with a 23% increased risk of developing CHD, which is close to my effect size, though with a narrower 95% CI (HR = 1.23, 95% CI, 1.16, 1.31, I^2 = 65%;(Smaardijk et al., 2019)). For women, the result derived from 28 studies and showed a risk estimate of 24% (HR = 1.24, 95% CI, 1.15, 1.33, I^2 = 68), which is about half that of my pooled effect size. One important reason for the discrepant findings is that in my review, the effect size in women subgroup was based on a very small number of reports (5) compared to Smaardijk et al. (2019) review. More recently, Bryant et al. (2020) examined whether age and gender modify the association between time-varying depressive symptoms and risk of all-cause and CVD mortality. In contrast to my results, they found that neither age nor gender moderate the association between depression and CVD mortality. but partly in line with Kouvari et al. (2019) results. Kouvari et al. (2019) conducted a prospective cohort study to examine the role of sex in the association between depressive symptomatology, incident and recurrent CVD events over 10 years period. The authors proposed that depressive symptomatology had an independent aggravating effect on the first and recurrent CVD events only in women.

5.6.7 **Comparison with previous reviews**

Appraisals of the literature have shown several studies similar to this review that have assessed depression in relation to either all CHD or specific components of CHD. The first systematic review, which is the highly cited review on this topic, was conducted by Rugulies (2002) incorporating 11 prospective studies published in the 1990s with 36,549 participants. The reviewer used only two databases

(Medline and PsycINFO) to retrieve eligible studies with MI and CHD as their main outcomes of interest. Angina pectoris was excluded from the author's criteria. Their main finding showed that depressed subjects had a 64% (RR = 1.64, 95% CI, 1.29–2.08) higher risk of developing CHD than non-depressed subjects. As a fundamental step in any systematic review, reviewers should assess and report the methodological quality of the included studies to supplement the reader with information about the strength of the body of evidence used to generate the estimated effect. Rugulies (2002) did not use a quality assessment tool or compute a methodological quality score for each of the included studies; hence, the likelihood of the inaccuracy of the reported estimated effect is unknown. Further, this publication did not explore publication bias. Soon after, Wulsin and Singal (2003) published a systematic review addressing the same research question with 10 studies and 27,231 participants. The reviewers had searched the same two databases as the previous review (i.e. Medline and PsycINFO). Since this publication synthesised evidence that spans around the same period (1993–2000) as Rugulies, it produced an identical effect estimate but with a narrower 95% CI (RR = 1.64, 95% CI, 1.41, 1.90). However, in contrast to Rugulies (2002), Wulsin and Singal (2003) explored the possibility of publication bias and suggested evidence of publication bias in their meta-analysis. Subsequently, Nicholson et al. (2006) performed a meta-analysis two times larger than the past reviews, incorporating 21 studies published before 2004 with 124,509 participants. The reviewers searched two search engines, including MEDLINE and Science Citation index citation tracking, without using relevant key databases, such as PsycINFO, which is specifically designed to access literature in psychology and related disciplines. Thus, potentially eligible papers may have been missed, which the authors acknowledged. As mentioned in the introduction, Nicholson et al. (2006) pointed out that about 50% of the studies conducted on this topic had poorly controlled for covariates and included crude RR or age-adjusted RR, resulting in an exaggeration of the estimated effect of depression on future CHD. After pooling the summary effect from 11 studies that had controlled for possible confounders, they found that depression was associated with a 90% (RR = 1.90, 95% CI, 1.49–2.42) increased risk of developing CHD. Fewer studies were available when these three reviews were conducted; hence, further analytical stratifications to explore the effect of depression on different subgroups were limited. Additionally, because a meta-analysis is essentially restricted to the adequacy and quality of

the available evidence, perhaps these early meta-analyses on this topic would be better described as informative reviews providing suggestive evidence for a positive association between depression and onset of CHD rather than precisely quantifying the estimated risk. This was evident in the magnitude of the estimated risk obtained from all three meta-analyses with the wide associated 95% CI, meaning that their estimated risk of depression was filled with great uncertainty and further investigation was required. In 2007, Van der Kooy et al. elaborated the previous work and identified 28 eligible studies using Medline and PsycINFO databases(Van der Kooy et al., 2007). Their primary aim was to estimate the risks of depression for a wide range of CVDs, including CHD, MI, stroke and other CVD. For CHD outcome, 16 studies were eligible to pool the risk estimate, which resulted in an effect size of 1.57 (95% CI, 1.35, 1.81), with a lower magnitude and a narrower 95% CI than past reviews. Van der Kooy et al. (2007) were also able to quantify the inconsistencies between studies using the I^2 test and provided evidence for statistical substantial heterogeneity between studies (I^2 = 62%), an important step that past reviews had not considered as this kind of test had not previously been introduced. Van der Kooy et al. (2007) performed additional analyses to explore the effect of depression on CHD subtypes and were first review to quantify an effect size for an association between depression and MI (OR = 1.60, 95% CI, 1.34, 1.92) based on eight studies with no evidence of statistical heterogeneity (I^2 = 0%). Nonetheless, all four reviews (Nicholson et al., 2006, Rugulies, 2002, Van der Kooy et al., 2007, Wulsin and Singal, 2003) included studies enrolling participants with CHD at the study baseline, which did not clearly enable readers to discern the depression as a pre-morbid risk factor and affected the magnitude of the true association (Gan et al., 2014). In the last decade, two meta-analyses on this topic were published adopting more strict inclusion criteria, including studies that focused on CHD free patients (Gan et al., 2014, Wu and Kling, 2016). Gan et al. (2014) search strategy included PubMed, Embase and Web of Science literature up to April 2014, without using a psychology-related database. They identified 30 potentially relevant studies enrolling 893,850 participants, becoming the largest meta-analysis on this topic to date. Methodological qualities of the eligible cohorts were assessed in accordance with the NOS tool. Their pooled RR demonstrated that depression was associated with a 30% increased risk of new onset CHD and MI (RR = 1.30, 95% CI, 1.22, 1.40; RR = 1.33, 95% CI, 1.18, 1.44, correspondingly). Heterogeneity between studies was

substantial (p = .000, I^2= 71.9). Further, they presented a cumulative meta-analysis and showed that the risk estimate stabilised from 2013 and remained unchanged after adding more recent large cohorts (Brunner et al., 2014, Gustad et al., 2014a), suggesting that adding more studies in future even with thousands of participants would produce similar results. The number of included cohorts (n=30) also made it possible to explore the effect of depression more extensively in different subgroups, including type of depression measurements, gender, age, follow-up duration and study location. However, the Gan et al. (2014) review contains important methodological problems that limit their results. First, the reviewers stated that only studies that have measured depression as a binary variable were considered, but they included ineligible studies with RR from studies modelled depression as a continuous or ordinal variable (Barefoot John and Schroll, 1996, Hawkins et al., 2014). Second, they included multiple publications from the same study populations (Anda et al., 1993, Brown et al., 2011, Ferketich et al., 2000, Hawkins et al., 2014). Third, their primary meta-analysis incorporated all independent reports of CHD subtypes (i.e. MI and fatal CHD) derived from one study. Therefore, they treated each report as a separate study (i.e. double counting of studies). Statistically, according to Borenstein et al. (2009), this is problematic, mainly because when computing the summary effect across studies, studies with more than one report will be assigned more weight than studies with only a single report, which will consequently affect the overall risk estimates (Borenstein et al., 2009). The latest review was carried out by Wu and Kling (2016). The authors used five search engines – MEDLINE, EMBASE, PsycINFO, ISI Web of Science and Scopus – up to August 2015. They also reviewed the references of the eligible papers and related review articles. The eligible outcomes in this review were only hard CHD endpoints (i.e. MI or fatal CHD) excluding composite CHD events involving angina pectoris. Their search identified 19 prospective cohorts with 323,709 participants. Because of the strict inclusion criteria in terms of the outcome of interest, several key studies in this area were omitted (Gump et al., 2005, Majed et al., 2012, Nabi et al., 2010a, Pequignot et al., 2013, Rahman et al., 2013, Scherrer et al., 2011). The methodological qualities of included cohorts were also assessed using the NOS tool. Compared to past reviews, Wu and Kling (2016) reported the lowest effect estimate of depression (RR = 1.22, 95% CI, 1.13, 1.32) but with a substantial amount of heterogeneity (p < .001, I^2 = 78.5).

My review covers the period after 2004; thus, it overlaps the latest two systematic reviews (Gan et al., 2014, Wu and Kling, 2016). I employed a similar search strategy to Wu and Kling's (2016) study, though I only used four databases (MEDLINE, EMBASE, PsycINFO, Web of Science) to retrieve potential studies. I also hand-searched the bibliography of related reviews (Gan et al., 2014, Smaardijk et al., 2019, Wulsin and Singal, 2003) and all relevant studies. I also extended the search to July 2020. The eligibility criteria for my review are stricter than all past reviews, as my research focused on participants who were free of CHD and stroke before study entry. Unlike Wu et al. (2016), I broadened the outcome to include various CHD and CHD related deaths following Gan et al.'s (2014) approach. I used a similar strategy to the last two reviews to assess the methodological quality of each included cohort. In comparison to Gan et al. (2014), I attempted to minimise the double counting of studies due to multiple reports of outcome by including only the HRs corresponding with the largest number of events and investigating the effect of depression on other independent reports of outcome within the same study by performing subgroup analyses. My search identified nine more recent cohorts, all of which were published after 2015. I also identified two major eligible studies (Mejia-Lancheros et al., 2014, Gafarov et al., 2013) that were omitted by the last two reviews. Nine cohorts (Ahto et al., 2007, Egede et al., 2005, Hawkins et al., 2014, Huang et al., 2013, Kamphuis et al., 2006, Marzari et al., 2005, Mittag and Meyer, 2012, Sun et al., 2013, Surtees et al., 2008a) that were published after 2004 and were included in the last two reviews were excluded from my study for reasons described in Section 3.2.1. Eventually, my meta-analysis comprised a much higher number of participants than Wu and Kling's (2016) review (> 10 times larger) and Gan et al.'s (2014) review (>3 times larger). Therefore, to the author's knowledge, the present meta-analysis includes all qualified studies, including those omitted by previous meta-analyses and most recent studies assessing the effect of depression on risk of incident CHD.

5.6.8 **Conclusion**

In conclusion, the results from this review provide strong evidence that baseline depression is independently associated with an increased risk of CHD, MI and angina, and it is unlikely to be influenced by the pre-existence of clinically apparent CHD and cerebrovascular diseases. The strong positive association was also evident between time-varying depressive symptoms and CHD incident.

Clinical depression was found to be a stronger predictor of CHD incident than depressive symptoms. However, on balance, this research was still unable to provide clear evidence of a linear association between depression and CHD risk, and further studies are warranted.

6 Depression and risk of HF in CVD free patients: A systematic review and meta- analysis

6.1 Introduction

6.1.1 HF

HF is a global pandemic affecting at least 26 million people worldwide and is increasing in prevalence and healthcare burden (Conrad et al., 2018, Savarese and Lund, 2017). A recent analysis of primary care data in the UK found that the absolute number of people living with HF increased by 23% between 2002 and 2014 from 750,125 to 920,616 (Conrad et al., 2018). In Scotland, the overall incidence and mortality rate of HF fell between 2008/09 and 2017/18, while a 23% increase was found in the hospital discharge rate, from 276 per 100,000 people to 342 per 100,000 people over the same period (Information Services Division, 2019). The health expenditure of HF accounts for approximately 1 million inpatient bed days, 2% of the National Health Service inpatient bed days and 5% of all emergency medical admissions to hospital, costing around £2 billion, which is equivalent to 2% of the total all National Health Service budget (National Institute for Health and Care Excellence, 2018).

HF has a poor prognosis, and despite advances in medical therapies, survival or improvement after a HF diagnosis remains poor. This highlighting the importance of prevention strategies and the need to target potential risk factors to avoid mortality and morbidity from HF. Common factors that contribute to the development of HF involve population aging and other modifiable CVD risk factors, such as hypertension, CHD and arrhythmias (Dunlay et al., 2009). Since depression has evolved as an independent risk factor for the new onset of stroke and CHD, it is plausible that depression may also be a risk factor for HF, and ongoing surveillance is required to determine its impact on HF aetiology.

6.1.2 **Depression in patients with HF**

Several studies have shown that HF is associated with an increased risk of depression. According to DeJongh et al. (2015) patients with HF are two to three times more likely to develop depressive symptoms than the general population. A large population-based study with 5,769 participants found that HF was an independent risk factor for depression and is associated with a 41% (05% CI 1.03, 1.94) increased risk of depressive symptoms and syndromes in this population (Luijendijk et al., 2010).

Compared to HF patients with no depressive symptoms, HF patients with depressive symptoms have worse outcomes across a broad range of events, including cardiac mortality, all-cause mortality, and other clinical conditions and healthcare utilisation. Rutledge et al. (2006) performed a meta-analysis to investigate the impact of depression on HF outcomes and reported that depressed patients with HF are more likely to experience increased healthcare utilisation, such as emergency room visits, healthcare costs and short- and long-term medical encounters, compared to HF patients without depressive symptoms. They also reported a two-fold increased risk of CVD mortality and all-cause mortality among HF patients with depression (Rutledge et al., 2006).

6.1.3 **HF in depressed patients**

In contrast to the large body of evidence supporting the detrimental effect of depression in HF populations, few studies have examined the association between depression and HF incidence in HF-free populations. The following section summarises these early studies and their main findings. Whooley et al. (1998) proposed that elderly women with six or more depressive symptoms have a three-fold (HR = 3.2 95% CI 1.3, 8.0) increased risk of death from HF compared to women with five or fewer depressive symptoms. However, a subsequent study conducted by Chen et al. (1999) rejected that symptoms of depression can be considered as risk factor for HF based on *p*-values from $\chi 2$ and t-statistics, which do not account for time to event. An epidemiological study conducted by Abramson et al. (2001) was the first cohort suggesting a strong association between depression and incidence of HF. This was a prospective cohort enrolling 4,538 individuals aged 60 years and older with isolated systolic hypertension (ISH) but free of HF at baseline.

Over 4.5 years, depression was independently associated with a substantial increase in HF risk (HR = 2.59 95% CI 1.57,4.27). This strong association remained stable after excluding HF cases that occurred within the first year of follow-up and when depressive symptoms were modelled as a time-dependent variable (Abramson et al., 2001). However, the participants in this study may have already had a high baseline risk of HF as they were elderly and had established ISH, both of which are risk factors for HF (Chen et al., 1999, Ekundayo et al., 2009). In addition, the study did not exclude previous history of MI, which may lead to an overestimation of depression risk. In a subsequent cohort, Williams et al. (2002) examined the association between depression and incidence of HF in 2,501 elderly participants aged ≥ 65 years who were free of HF at baseline. In this study, the authors identified depressive symptoms using the CES-D with a high cut-off score of ≥ 21, which approximates a clinical diagnosis of depression. They found that depression was not significantly associated with increased risk of HF (HR = 1.52 95% CI 0.94, 2.43). However, in a subsequent analysis, they showed that depression was an independent risk factor for HF in women but not in men. In view of these inconsistent study findings, I conducted a systematic review and meta-analysis to investigate the association between depression and the initial onset of HF in CVD free population at study entry.

6.2 Aim

This chapter systematically reviews and reports a meta-analysis of prospective cohort studies that examined the association between depression and HF incidents in CVD-free patients.

6.2.1 Hypothesis

1- Depression is associated with an increased risk of HF in CVD-free patients.

2- Depression increases the risk of HF in a dose-response manner.

6.3 Method

Full descriptions of the methods used for this review and meta-analysis were provided in **Chapter 2, Section 2.1, Systematic review and meta-analysis.**

The cohort conducted by White et al. (2015) is a population-based cohort that used an established data from the Veterans Aging Cohort Study. This cohort included data about individuals with or without HIV infection matched on age, sex, race/ethnicity and clinical site, extracted from the US Department of Veterans Affairs (VA) administration. White et al. (2015) performed a separate analysis to investigate the incidence of HF risk in HIV-infected participants and in HIV-uninfected participants. This review considered only data for HIV-uninfected participants, including cohort size, clinical characteristics and the calculated HR estimated risk of depression.

6.4 **Results**

Overall, the analysis includes three studies comprising 2,200,308 participants and an average follow-up of 10.13 years. Chapter 3 provided a full description of the search and identification process of the included cohorts and a summary of the studies. Table 6-1 summarises the main characteristics of the included studies. In short, two studies were conducted with cohorts in European countries and had a long follow-up duration (≈ 13 years) (Daskalopoulou et al., 2016, Gustad et al., 2014b). One study was performed in the US with a shorter follow-up duration (6 years) (White et al., 2015) and one was an international study where participants recruited from 21 economically diverse countries with a follow-up duration of 14 years. Two studies used the ICD codes with or without antidepressant prescriptions to identify patients with clinical depression (Daskalopoulou et al., 2016, White et al., 2015). Rajan et al. (2020) used the short form of the diagnostic interview and Gustad et al. (2014b) used a validated SRS to identify depression cases. Only one study investigated the dose-response relation between depressive symptoms and HF (Gustad et al., 2014b). The primary outcome, new-onset HF, was identified according to the ICD codes extracted from electronic medical records. The total number of HF cases from the four cohorts was 20,268. Three cohorts (Daskalopoulou et al., 2016, Rajan et al., 2020, Gustad et al., 2014b) included men and women, whereas the study by White et al. (2015) was almost entirely male (96%). Only one study reported a small loss to the follow-up proportion (0.3%) (Gustad et al., 2014b). All three studies estimated the effect size of depression using HRs, providing a consistent measure.

Table 6-1 Characteristics of the included cohort studies

Study	Location	N	Men (%)	Age (years) Mean/median/range	Length of follow-up (years)	Exposure measure	Outcome	Outcome measure	Cases (n)	Confounder adjustment
(Daskaloupoulou et al., 2016)	UK EU	1,937,360	NA	≥30	13 years 1997-2010	Medical records of CD/AD	HF	Medical records according to the ICD 10 (I50, I11.0, I13.0 and I13.2), death	9397	Age, sex, smoking, SBP, diabetes, cholesterol, and socio-economic status
(Gustad et al., 2014b)	Norway, EU	62,567	46.8	≥18	13 years 1995-2008	21-item HADS ≥11	HF	Medical records according to ICD 9 (428) and ICD 10 (I50.0, I50.1 and I50.9)	1499	Age, sex, marital status, education, smoking, physical activity, BMI, total cholesterol, diabetes mellitus, resting HR, SBP, alcohol, serum creatinine, time-dependent adjustment for AMI during follow-up.
(Rajan et al., 2020)	Multinational	145,862	58	35-70	14 years 2005-2019	CIDI-SF; cut-off point 4 or more DS	HF	Self-reported through standardised form, household interviews, medical records, death certificates, and other sources	582	Age, sex, urban/rural residence, educational attainment, use of statins, disabilities former and current smoking and alcohol use, HTN, diabetes, and social isolation index
(White et al., 2015)	USA	54519	96	48	6 years 2003-2009	1 or 2 inpatient outpatients for CD of MDD according to ICD-9 (296.2x and 296.3x)	HF	Medical records according to ICD-9 (428.xx, 429.3, 402.11, 402.91, 425.x))	8791	Age, sex, race/ ethnicity, BMI, HTN, diabetes mellitus, LDL-c, HDL-c, triglycerides, statin use, hemoglobin, renal function, atrial fibrillation, atrial flutter, smoking status, alcohol abuse or dependence, cocaine abuse or dependence,

Abbreviation: AD, antidepressants; BMI, body mass index; CD, clinical diagnosis; HADS, hospital anxiety depression scale; HDL-c, high density lipoprotein cholesterol; HF, heart failure; HTN; hypertension; ICD, International classification of diseases; LDL-c, low density lipoprotein cholesterol; MDD, major depressive disorders, SBP, systolic blood pressure; UK, united kingdom; USA, United States America.

Depression and risk of HF

As shown in Figure 6-1, depression is associated with a 17% (HR = 1.17, 95% CI 1.08, 1.28, *P* <0.0002) increased risk of HF incidence in CVD free participants, with no significant amount of heterogeneity (chi-square *P* = 0.77 and I^2 statistics of 0%). In this analysis, out of four studies, two studies showed a positive association, while the other two have a null result. Notably, the pooled estimated risk was mostly driven by cohorts that reported a positive association conducted by White et al. (2015) and Daskalopoulou et al. (2016) as, altogether, they carried more than 80% of the overall weight.

The interpretation of funnel plots (

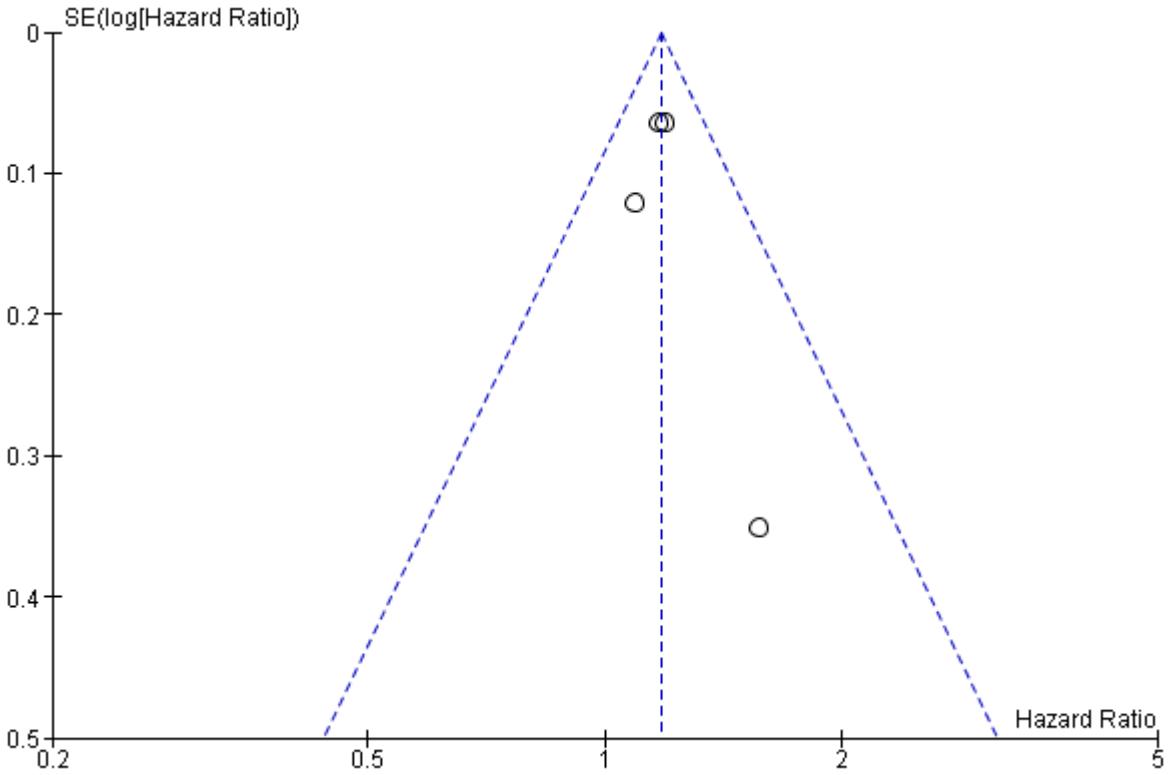

Figure 6-2) to investigate risk of publication bias was limited due to the small number of pooled results in this analysis. The removal of each study in turn provided similar estimates of HR ranging between 1.16 and 1.19.

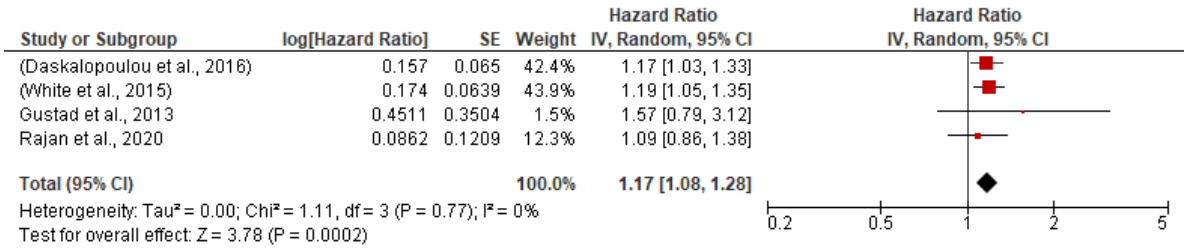

Figure 6-1 Forest plot showing the adjusted HR of HF incidence for depressed individuals compared with non-depressed individuals in 4 cohorts
Abbreviations: HF; heart failure; SE, standard error

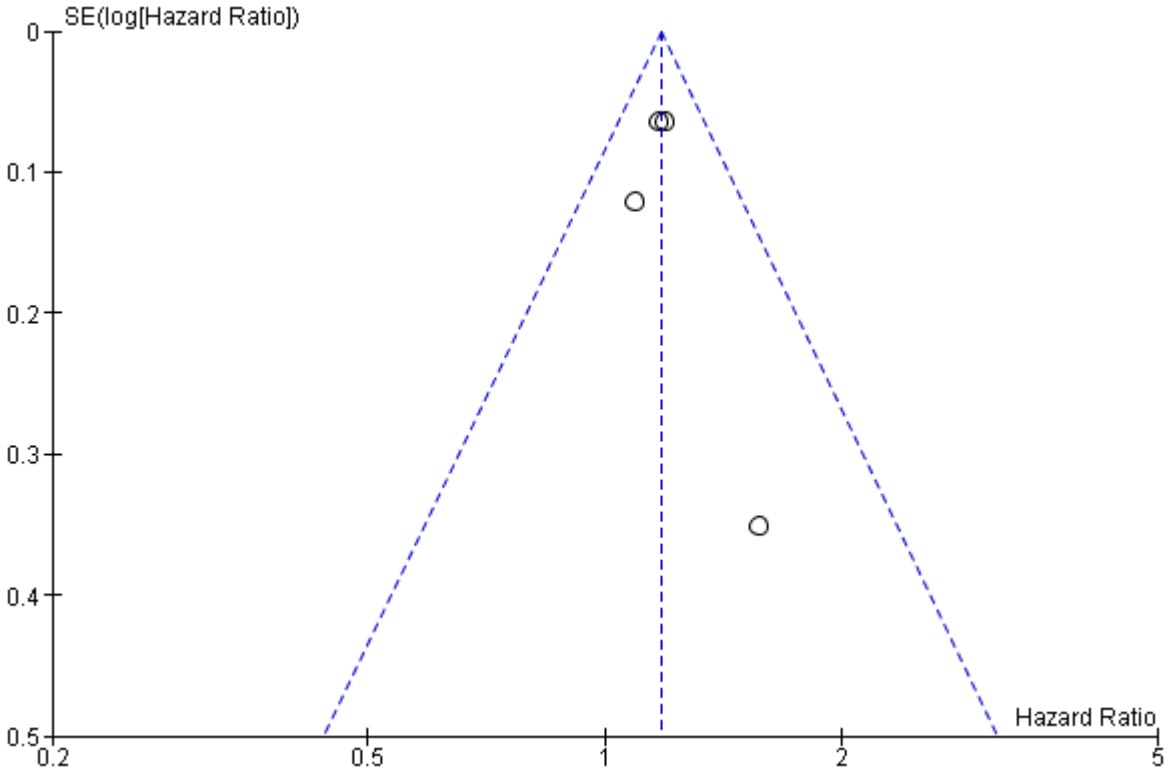

Figure 6-2 Funnel plot from 4 cohorts investigated the association between depressions and first-incidence of HF. SE, standard error

6.5 Discussion

This meta-analysis of four cohorts provides evidence supporting an association between depression and an increased risk of HF incident (HR = 1.17 95% CI 1.08, 1.38) in CVD free participants. However, due to low power of this analysis (the total included number of studies is small), these results should be considered with caution.

Only a few studies published between 2005 and 2020 investigated the relationship between depression and incidence of HF, plus their findings were conflicting. For example, Kamphuis et al. (2006) studied the relationship between depressive symptoms and CVD using data from Finland, Italy and the Netherlands. The researchers enrolled 799 men, aged 70–90 years, free of CVD at baseline and followed them for up to 10 years for the first CVD outcome. Their main findings showed that every five-point increase in depressive symptoms was associated with a 16% (HR = 1.16 95% CI 1.00, 1.35) increased risk of developing HF. By contrast, in a 10-year prospective study with 4,114 elderly participants who were free of HF at baseline, van den Broek et al. (2011) found no evidence that depression was associated with an increased risk of new-onset HF (HR = 1.08 95% CI 0.92–1.26). A subsequent large prospective study of 236,079 VA participants who had no previous history of CVD and were aged between 50 and 80 years demonstrated that individuals with MDD had a 56% (HR = 1.56 95% CI 1.45, 1.67) increased risk of HF incidence compared to those without MDD (Garfield et al., 2014). More recently, Khodneva et al. (2019) conducted a prospective cohort study to investigate the association between depressive symptoms and risk of first HF hospitalisation among community dwelling individuals (aged ≥45 years) who were free of HF and CHD at study baseline. The authors demonstrated that the risk differs by the type of HF based on ejection fraction: they found that depressive symptoms were independently associated with future risk of first hospitalization for HF preserved ejection fraction (HR= 1.54, 95% CI 1.06-2.22), but not for HF reduced ejection fraction.

Table 6-2 summarises the studies that investigated the relationship between depression and incidence of HF. The table shows that the magnitude of the HRs varies considerably across the studies, which may be due to several reasons. One reason is the varied population between the studies, as some focused on elderly

populations (Abramson et al., 2001, Chen et al., 1999, Kamphuis et al., 2006, Khodneva et al., 2019, van den Broek et al., 2011), while others included only men (Kamphuis et al., 2006), only women (Whooley et al., 1998) or patients with specific health conditions (Abramson et al., 2001). In this meta-analysis, the population in the White et al. (2015) study was almost entirely men (96%), and evidence shows that the incidence of HF is generally higher in men than in women at all ages (Mehta and Cowie, 2006). Therefore, the pooled estimates of HRs may be affected by the unequal male/female proportion in this study. Another possible reason for discrepancies is the different diagnostic tools used to identify depression cases. As is known, the diagnosis of depression based on the gold standard method means that only cases with more severe depressive symptoms will be considered, while other screening tools such as the SRS are likely to capture severe symptoms as well as mild to moderate symptoms. This may be an important issue when examining the relationship between depression and HF. Unlike stroke and CHD, where the risk conferred by depression has been well documented in relation to moderate and more severe depressive symptoms, it is unclear whether the same applies to HF.

Unfortunately, I was unable to examine whether a dose-response relationship existed between depression and HF, as only one of the included studies provided such information (Gustad et al., 2014b). Two other cohorts that had not met my inclusion criteria (Abramson et al., 2001, Kamphuis et al., 2006) also explored whether a dose-response relation exists. All three studies reported that depression increases the risk of HF in a dose-response manner, although evidence for significant association was only observed for high levels of depressive symptoms, which may indicate that depressive symptoms need to reach a clinical threshold to be considered a risk factor for HF. However, this finding was not replicated by other studies (Williams et al., 2002). Overall, it is still early to draw a firm conclusion as the effect of depression may differ substantially following addition of studies in the future.

Because the results of my meta-analysis derived largely from cohorts that examined the risk of developing HF in relation to clinical depression (i.e. severe depressive symptoms), they cannot be applied to depression of mild to moderate severity.

6.6 Conclusion

This study found that depression was associated with an increased risk of HF incidence in a CVD-free population. The results from this review and meta-analysis add to the growing body of evidence suggesting that depression is a risk factor of HF independent of the main precursors for HF (i.e. CHD). However, because most studies relied on clinical diagnosis as a criterion to measure depression the finding is more likely to reflect the impact of clinical depression rather than depressive symptoms. Further research confirming this finding and investigating the role of depression in the pathological process underlying HF is warranted.

Table 6-2 summary of studies examined the association between depression and HF morbidity and mortality

Study	Study Design	Study population	N	Exp	OC	FU*	HR (95%CI)	Comments
(Abramson et al., 2001)	Prospective cohort	Elderly free of HF with ISH	4538	DS	Incident HF	4.5	2.59 (1.57-4.27)	
(Chen et al., 1999)	Prospective cohort	Elderly free of HF and CHD	1749	DS	Incident HF	10	NA	Risk was measured by $\chi 2$, *P*- = 0.65
(Garfield et al., 2014)	Retrospective cohort	Elderly VA free of CVD	236,079	MDD	HF-related death	6	1.56 (1.45–1.67)	
(Heo et al., 2020)	Prospective cohort	Participants with HF	94	DS	HF symptoms	12 months		Baseline DS strongly predict 12-month HF symptoms *P* <0.001
(Kamphuis et al., 2006)	Prospective cohort	Men elderly, free of CVD	799	DS	Incident HF	10	1.16 (1.00–1.35)	
(Khodneva et al., 2019)[a]	Prospective cohort	Community dwelling Free of CHD and HF	22,465	DS	Incident HF hospitalisation	11	1.54 (1.06-2.22)	Risk was evident only for HFpEF but not for HFrEF
(Luck-Sikorski et al., 2015)	Prospective cohort	Elderly	1,815	DS	HF-related death	9	NA	HR was calculated based on sex. Risk was significant for men but not for women
(Patel et al., 2020)	Retrospective cohort	Patients discharge with HF	3,500,570	MDD	90-day HF readmission	90 day	0.99 (0.97–1.01)	

Study	Study Design	Study population	N	Exp	OC	FU*	HR (95%CI)	Comments
(van den Broek et al., 2011)	Prospective cohort	Elderly free of HF	4,114	DS	Incident HF	11	1.08 (0.92-1.26)	
(Whooley et al., 1998)	Prospective cohort	Elderly with CVD	7518	DS	HF-related death	7	3.2 (1.3-8.0)	
(Williams et al., 2002)	Prospective cohort	Elderly free of HF	2501	DS	Incident HF	14	1.52 (0.94-2.43)	

Abbreviations: CHD, coronary heart diseases; CVD, cardiovascular diseases; DS, depressive symptoms; EXP, exposure; FU, follow-up; HF, heart failure; HFpEF; heart failure preserved ejection fraction; HFrEF; heart failure reduced ejection fraction; HR, hazard ratio; ISH, isolated systolic hypertension; MDD, major depressive disorders; NA, not applicable; OC, outcome; VA, Veterans Affairs; * follow-up demonstrated in years unless indicated; [a] Study was a conference abstract.

7 Antihypertensive drugs and risk of depression

7.1 Introduction

Evidently, all antihypertensive drug classes are deemed to be effective in controlling BP, thereby recommended by clinical guidelines as first- or second-line therapy to manage hypertension. Since hypertension is a chronic health problem, these drugs are intended for long-term use with the ultimate objective of preventing CVD and end organ damage. In the introduction of this thesis, I compiled evidence for a long-standing controversy, dating from as early as 1967 (Waal, 1967), about a possible role of antihypertensive drugs in the pathogenesis of depression. Promising findings suggesting that antihypertensive drugs may protect against depressive symptoms co-exist with negative reports of increased risk of depression. Based on my findings in Chapters 4–6, one in five people who have experienced depression during their lifetime is likely to develop CVD. The same figure has been reported in CVD patients in relation to depression incidence. The data shows that for every five CVD patients, at least one will meet the criteria for MDD, which contributes to poor cardiovascular outcomes for such patients. Accordingly, it is reasonable to assume that factors associated with an increased risk of depression would indirectly heighten the risk of subsequent CVD and poor health outcomes. Given that antihypertensive drugs constitute one of the cornerstone therapies for patients at high risk of CVD and those with established CVD, it is crucial to understand the impact of this type of treatment on depression. I therefore aim to investigate the association between different antihypertensive drug classes and depression.

Figure 7-1 provides a theoretical illustration of the role of four major classes of antihypertensive drugs in depression based on pre-clinical evidence. I hypothesised that BB and CCB are associated with an increased risk of depression, as they interfere with BDNF, neuronal survival and neuronal plasticity, while ACEI and ARB are associated with a reduced risk of depression, as they act as anti-inflammatory agents at the circulatory and neuronal levels. In the absence of compelling evidence linking diuretics to depression, it is plausible to hypothesise that they have no effect on depression.

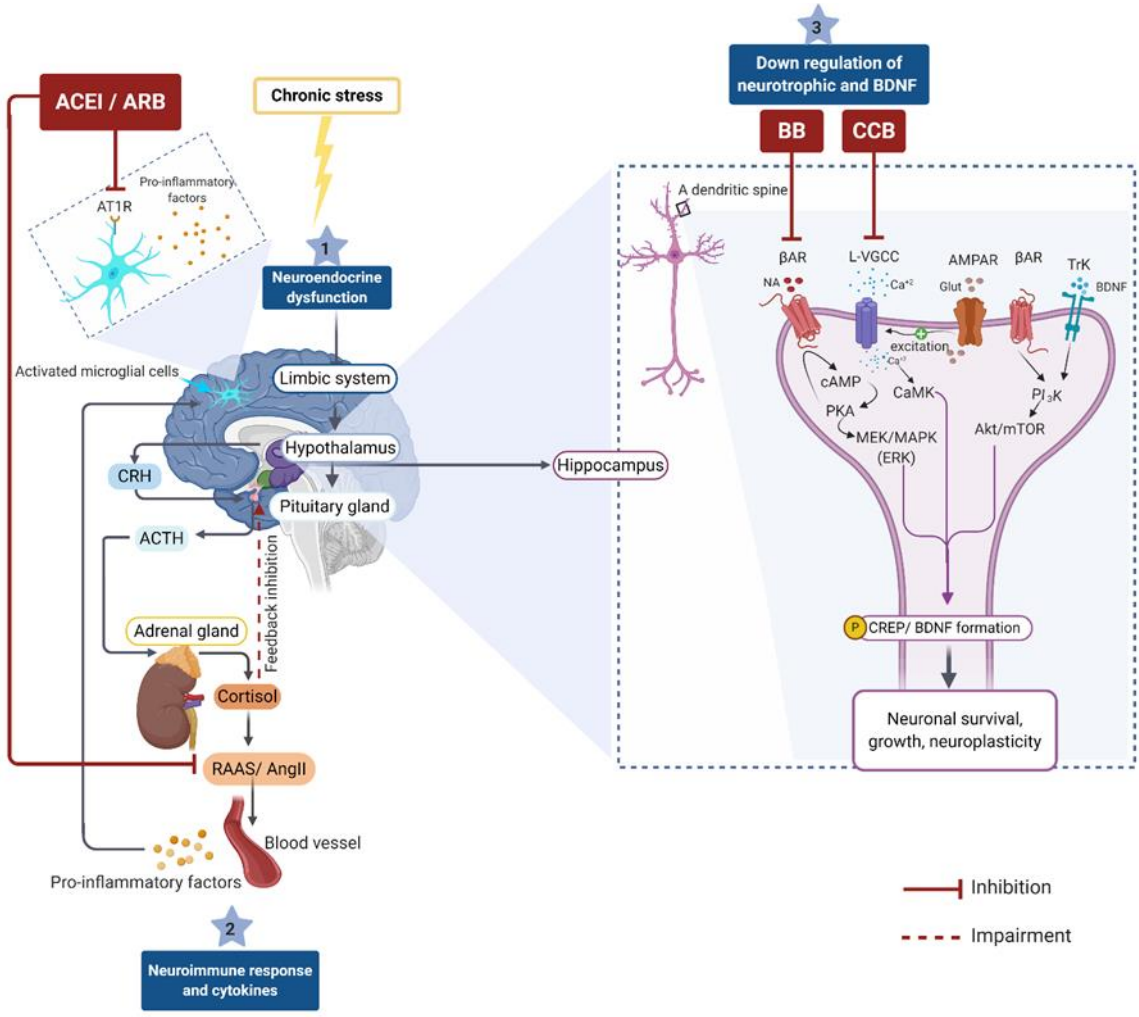

Figure 7-1 Illustrations of the main pathways linked to depression that are likely to be modulated by antihypertensive drugs

Theoretically, ACEIs and ARBs may produce a beneficial effect in depression as they suppress the RAAS and AT1R respectively reducing the stress sensitivity of HPA-axis and therefore decrease HPA—axis hyperactivation during stress, which corresponds with the neuroendocrine dysfunction theory of depression (1). ACEIs and ARBs may also act as anti-inflammatory agents reducing neuronal inflammation associated with depression, corresponding with the inflammation theory of depression (2). By contrast, CCBs and BBs may disrupt the normal process of synaptic plasticity and neurogenesis, hence may increase risk of depression which corresponds with the down regulation of BDNF and nerve growth theory of depression (3). Abbreviations: ACEI, angiotensin converting enzyme inhibitors, ACTH, adrenocorticotropic hormone; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; Akt, protein kinase B; ARB, angiotensin receptor blocker; AT1R; angiotensin type-1 receptor, Ang II, angiotensin; βAR, beta-adrenergic receptor; BB, beta-blocker; BDNF, brain derived neurotrophic factor; Ca^{+2}, calcium; cAMP, cyclic adenosine monophosphate, CaMK; Ca2+/calmodulin-dependent protein kinase; CCB, calcium channel blocker; CREB, cAMP-responsive element-binding protein CRH, Corticotropin-releasing hormone; ERK, extracellular signal-regulated kinase; Glut, glutamate; L-VGCC, L-type voltage calcium channel; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; NA, noradrenaline; PKA, protein kinase A; PI_3K,phosphoinositide-3 kinase, RAAS, renin angiotensin aldosterone system; TrK, tropomyosin receptor kinase

7.2 Aim

The aim of the study is to test for association between antihypertensive drugs use and incident depression defined by a first-ever prescription of antidepressants after commencement of antihypertensive therapy. A secondary aim was to study the association between antihypertensive drug exposure defined by cumulative daily defined dose (cDDD) of the five anti-hypertensive classes and incident depression.

7.2.1 Hypothesis

1- CCB and BB as monotherapy or as part of polytherapy are associated with an increased risk of incident depression compared to ACEI.

2- There will be a dose–response relationship between the defined daily dose (DDD) of CCB and BB and the risk of depression.

7.3 Methodology

7.3.1 Study setting and population of the GBPC

The study population includes all patients attending the GBPC between January 2005 and March 2013. Further information on the study population and setting has been provided in Section 2.1.7

7.3.2 Study design

This study was a retrospective cohort study of patients attending a specialist hypertension clinic who were newly prescribed antihypertensive drugs. All patients between the ages of 18 and 80 years at the time of their first prescription were included in the study. Two analyses were performed and described below.

7.3.2.1 Antihypertensive monotherapy and risk of depression

In this analysis, the exposure period to antihypertensive monotherapy for all eligible patients was fixed at one year. This time window starts from the month of their first fill of an antihypertensive drug prescription at any time point between January 2005 and March 2012 and extends to 12 months. At the end of this period, follow-ups commence and continued until the first prescription of antidepressants (study outcome), the time of death or up to March 2013 (end of the study). A graphical chart of the monotherapy study design is represented below (Figure 7-2).

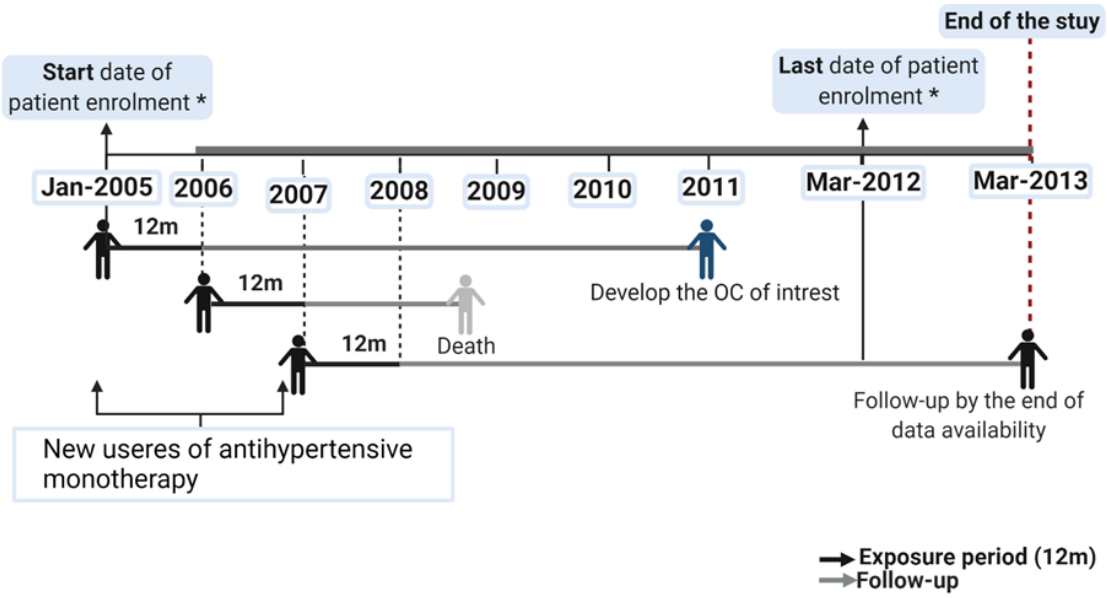

Figure 7-2 Graphical chart for the monotherapy study design

7.3.2.2 Antihypertensive drugs as monotherapy or as part of polytherapy and risk of depression

In this analysis, eligible patients were identified between January 2006 and March 2013. The participants were newly commenced on antihypertensive drugs, which was defined as not having been prescribed any antihypertensive drugs for six months before the index date of the first prescription. The first six months after the index date was considered a treatment period. Patients who died or developed depression within this period were excluded. The cumulative number of antihypertensive drugs, either those had discontinued or changed to another drug class during the treatment period was calculated. They were also numbered in order based on their sequence.

7.3.3 Inclusion criteria

For the monotherapy analysis, patients were eligible for inclusion if they were between 18 and 80 years of age at the time of the first prescription of antihypertensive medication, if they newly started antihypertensive monotherapy and if they continued to be on the same single medication over the exposure period. The patients should have had no previous history of an antidepressant prescription. I also excluded subjects with a recorded prescription of antihypertensives before January 2005, those who were on multiple antihypertensive medications at any point during the exposure period, patients who had developed depression (recorded first prescription of antidepressants), those who died during the antihypertensive exposure period and patients who started antihypertensive treatment after March 2012. As shown in Figure 7-3, of the 9070 patients screened, 2406 were eligible to be included in this analysis.

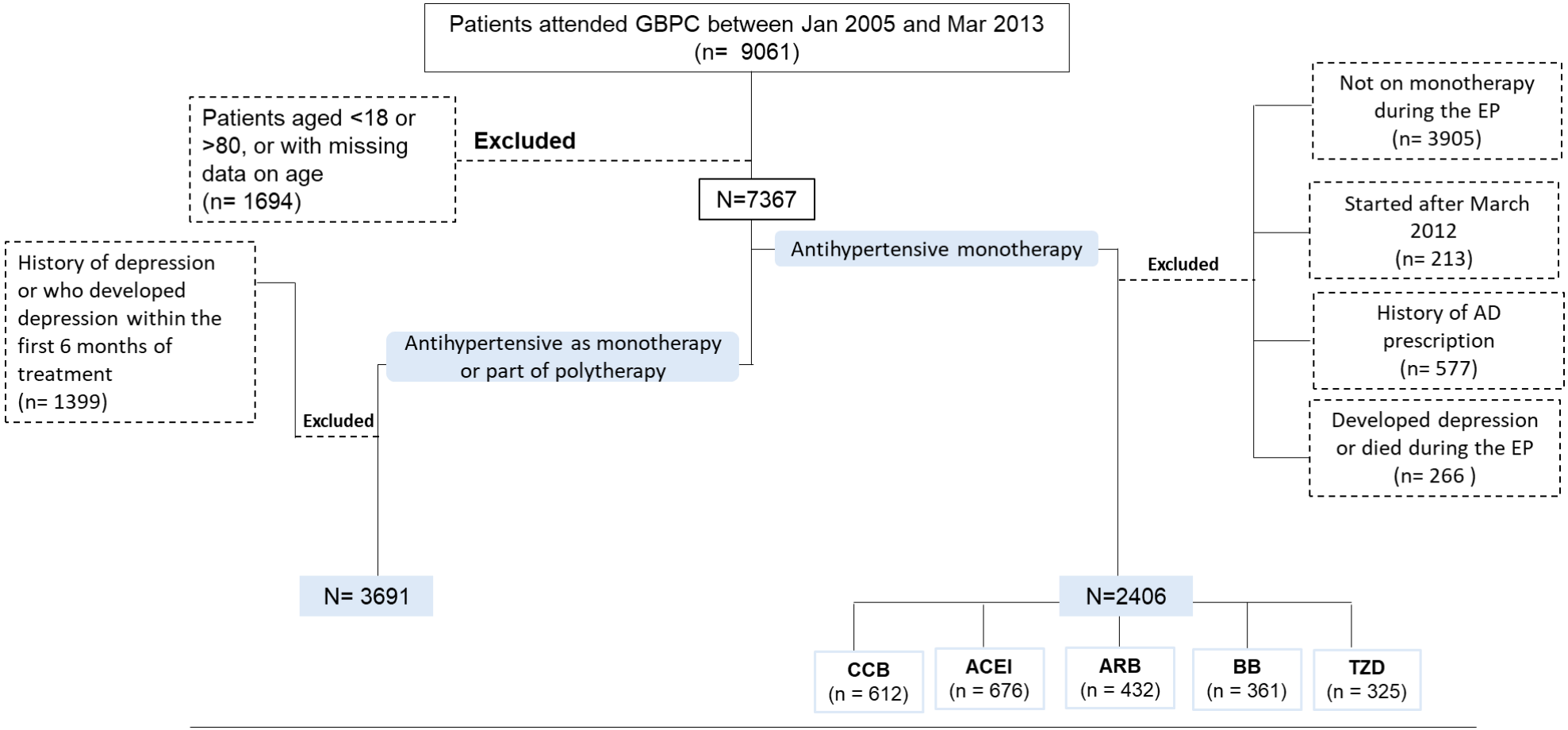

Figure 7-3 Flow charts for patient's inclusion

7.3.4 Definitions

7.3.4.1 Exposures

For the monotherapy analysis, exposure was defined as a monotherapy prescription of any of the following antihypertensive medications: CCB, BB, ACEI, ARB and TZD. In the case of polytherapy, the definition of exposure was extended to include other classes of antihypertensive drugs, such as alpha blockers and centrally acting agents. CCBs were further devided into dihydropyridine and non-dihydropyridine, while diuretics were also stratified into spironolactone and mineralocorticoids.

7.3.4.2 Outcome

The main outcome in this study was depression defined by initiating antidepressant medication, including TCA, SSRI, MAOI and 'other antidepressants'.

7.3.5 Assessemnt of study quality

I applied the NOS tool to evaluste the quality of the present cohort in a similar way as descriped in section 2.1.5.

7.3.6 Statistical analysis

Details on the statistical packages and tests were used to summarise and present data were previously described in section 2.2.3 For the monotherapy cohort analysis, Cox proportional hazards models were used to estimate the risk of developing depression among the five monotherapy drug classes of antihypertensive drugs. In this analysis, outcome was treated as a binary outcome (presence/ absence of depression). The time to event was calculated in years from the last month of the exposure period to either the first prescription date of antidepressant, date of death, or the last follow-up date for the study. Model 1 was adjusted for age at first prescription and gender. Model 2 was further adjusted for the other covariates including BMI, smoking, SBP, CCI, cholesterol and eGFR. The ACEI group was the reference group. Proportionality assumptions was checked by inspection of log minus log plots and testing of Schoenfeld residuals.

If a causal relationship indeed exists between any antihypertensive drug and depression, a trend toward elevated risk of depression is expected to be observed with higher levels of antihypertensive drugs. I therefore investigated the dose-response relationship between each antihypertensive drug class and depression using escalating levels of antihypertensive DDD. Because the DDD are likely to be changed over the exposure period, and there are likely to be short-term and long-term users, I calculated the cumulative DDD (cDDD) for each patient, representing the total exposed DDD dispensed monthly during the exposure period. I chose to classify the cDDD into tertiles, approximately equal in sizes, instead of a continuous measure for two reasons. First, the DDD data was positively skewed in this study. Second, to enable a comparison between groups that had been exposed to low, moderate and high cDDD. In this contest, the referent group in Cox regression analysis was the lowest cDDD tertile within the drug class. I then used stepwise backward regression analysis to obtain the most parsimonious model. All variables were included in the 'variable list' and the significant levels for entry and removal were set at 0.15 and 0.2 respectively, as a conservative approach. In the next step, the algorithm attempts to drop one of the variables with *p*-value ≥0.2, one at a time. The best final model includes all covariates with *p*-value ≤0.15 at the chosen α significance level of 0.05. This stepwise procedure has been criticised on many counts. One of the most noted potential drawbacks is that it may not be guaranteed to reveal the best subset variables within a model. Additionally, models identified by stepwise methods have an inflated risk of capitalising on chance features of the data which may then fail when applied to new datasets. On the other hand, this is a commonly used procedure which is easily implemented and intuitive.

For the polytherapy analysis, a similar analytical approach was used to examine the association between the index antihypertensive drug and depression incidence. Cox proportional hazard analysis was performed to estimate the depression incidence in comparison to the ACEI group. Models 1 and 2 were adjusted for the same covariates previously mentioned; however, in this context, the number of antihypertensive drugs was also added to Model 2 as a covariate. In order to conduct a more inclusive analysis that is relevant to real-life where patients tend to be prescribed multiple drugs a generalised estimating equations method was employed. This overcomes the correlation between patients who

appear in the data multiple times when they are prescribed a new antihypertensive drug. A sequence variable that indicates the order by which a new agent was prescribed was used to inform the model of the repeated measure. The GEE analysis in polytherapy study permits that examination of association between the index prescription of antihypertensive drug and risk of depression in the presence of other concomitant antihypertensive therapy. The GEE model was estimated with a binomial outcome (presence/absence of new-onset depression) distribution and a logit link. The univariate and multivariate models were adjusted for the same prespecified covariates. This type of analysis accounts for the within-subject variable, in this context defined as repeated admission (as a proxy for each time a new antihypertensive drug class was introduced) and, therefore, allows the use of all available data for all eligible patients.

7.4 Results

7.4.1 Antihypertensive drugs and risk of depression: monotherapy analysis

7.4.1.1 General characteristics of the GBPC study population

Table 7-1 summarises the clinical characteristics of the 2406 patients involved in the monotherapy analysis. The study population was middle aged at the initiation of their treatment (mean age 51 ± 14), hypertensive (SBP/DBP = 157 ± 24 /93.79 ± 12 mm Hg), and overweight (BMI = 28.45 ± 5.4), with an approximately equal sex distribution (female, 50.9%). About 35% were smokers, 68% had at least stage 3 chronic kidney disease (CKD) and more than half (57%) had comorbid conditions at baseline. The average follow-up was 4.3 years.

Table 7-1 Baseline characteristic of the GBPC population on antihypertesive monotherapy during the first 12 months window (n=2406)

Variable	M (SD)/ N (%)
Age at first prescription (years)	51.12 (14.00)
SBP (mmHg)	157 (24.4)
DBP (mmHg)	93.79 (12.52)
BMI	28.45 (5.4)
Cholesterol	5.78 (1.1)
Gender	
Male	1181 (49.1)
Female	1225 (50.9)
Smoking	
Non-smoker	1553 (64.5)
Smoker	853 (35.5)
Kidney function	
eGFR (≥60ml/min)	394 (16.4)
eGFR (<60ml/min)	1647 (68.5)
Charlson comorbidity index score	
0	1034 (43)
1	633 (26.3)
>1	739 (30.7)
N of prescriptions during the EP	
1-3	948 (39.4)
4-6	866 (36)
≥7	592 (24.6)

BMI, body mass index; DBP, diastolic blood pressure; eGFR, Estimated glomular filtration rate; EP, exposure period; SBP, systolic blood pressure. Continuous data are presented in mean (M)/ slandered deviation (SD), Categorical data are presented in numbers (%).

7.4.1.2 General characteristics of the study population grouped by antihypertensive drug class

The baseline characteristics of the study population stratified by antihypertensive drug class are presented in Table 7-2. The mean age of the different antihypertensive treatment groups varied, with patients on ACEI having the youngest mean age (48.7 years), while those in the TZD group had the oldest mean age (53.3 years). Patients on CCB, BB and TZD were predominantly female, while those on ACEI and ARBs were mainly male. There were significant differences between the groups in terms of baseline SBP/DBP, with patients receiving ARB showing the highest SBP/DBP measures (160.5 ± 24.8/95.3 ± 12.6). About half of the patients (51%) who were treated with ACEI had a CCI score of zero reflecting no comorbidities, while 57% patients on other antihypertensives had a CCI score of at least 1. Patients receiving BB and ACEI were more likely to be on treatment for more than 6 months, as indicated by the number of prescriptions (30.2% and 27.7%, respectively) compared to other antihypertensive groups (< 25%).

Table 7-2 Baseline characteristic of the study population (n=2406) stratified by monotherapy drug regimen

Variable	CCB (N=612)	BB (N=361)	ACEI (N=676)	ARB (N=432)	TZD (N=325)	*P*-value
Age at first prescription (years)	52.6 (13.7)	50.48 (14.41)	48.73 (14.3)	51.64 (13.5)	53.3 (13.43)	**0.000**
Female sex	321 (52.5)	194 (53.7)	314 (46.4)	213 (49.3)	183 (56.3)	**0.023**
SBP,mmHg	159.83 (25.13)	153.88 (24)	154.61 (24)	160.50 (24.86)	158.75 (22.7)	**0.000**
DBP,mmHg	94.34 (13.21)	92.45 (12.52)	92.82 (11.96)	95.38 (12.69)	94.15 (11.79)	**0.003**
BMI	28.37 (5.3)	28.64 (5.8)	27.73 (5.22)	28.75 (6)	28.7 (5.1)	0.36
Cholesterol	5.82 (1.13)	5.68 (1)	5.78 (1.12)	5.8 (1.06)	5.8 (1.07)	0.45
Smoking	230 (37.6)	138 (38.2)	244 (36.1)	137 (31.7)	104 (32)	0.14
eGFR (< 60 ml/min)	403 (78.9)	250 (81.4)	463 (83.1)	305 (80.1)	226 (79.3)	0.44
Charlson index score						
0	237 (38.7)	155 (42.9)	345 (51)	182 (42.1)	115 (35.4)	
1	166 (27.1)	101 (28)	149 (22)	115 (26.6)	102 (31.4)	**0.000**
>1	209 (34.2)	105 (29.1)	182 (26.9)	136.3 (31.3)	108 (33.2)	
N of prescriptions during the EP						
1-3	226 (36.9)	141 (39.1)	257 (38.0)	166 (38.4)	158 (48.6)	
4-6	247 (40.4)	111 (30.7)	232 (34.3)	159 (36.8)	117 (36.0)	**0.000**
≥7	139 (22.7)	109 (30.2)	187 (27.7)	107 (24.8)	50 (15.4)	

ACEI, Angiotensin converting enzyme inhibitor; ARBs, Angiotensin II receptor blockers; BB, β-blockers; BMI, body mass index; CCB, calcium channel clocker; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; EP, exposure period; N, number; SBP, systolic blood pressure; TZD, thiazide diuretics. X2 test and 1-way ANOVA test were used for categorical and continuous variables respectively. Continuous data are presented in mean (M)/ slandered deviation (SD), Categorical data are presented in numbers (%).

7.4.1.3 General characteristics of the study population grouped by the presence or absence of new-onset depression

Table 7-3 presents the clinical characteristics of the 2406 participants according to whether or not they developed depression. The baseline characteristics, such as age, SBP, DBP, CCI and eGFR, were comparable between the two outcome groups. However, other potential risk factors, such as BMI and smoking, were more frequent in patients who developed depression. As expected, females were over-represented in the depressed patients group (60.4%, $p < 0.000$). Almost one-third of the participants who developed depression were on CCB, 21% on ACEI, 19% on ARBs, 15.5% on BB and 12.8% on TZD.

Table 7-3 Baseline characteristic of 2406 patients on antihypertensive monotherapy during the first 12 months window stratified by the main outcome

Variable	Outcome		*p*-value
	No depression N=1865 (77.5)	depressed N=541 (22.5)	
Age at first prescription (years)	51.22 (14.08)	50.75 (13.87)	0.49
SBP	157.54 (24.4)	157.14 (24.25)	0.73
DBP	93.92 (12.4)	93.32 (12.72)	0.32
BMI	28.26 (5.14)	29.13 (6.47)	**0.004**
Cholesterol	5.7 (1.08)	5.8 (1.10)	0.59
Gender			
Male	967 (51.8)	214 (39.6)	**0.000**
Female	898 (48.2)	327 (60.4)	
Smoking			
Non-smoker	1227 (65.8)	326 (60.3)	**0.018**
Smoker	638 (34.2)	215 (39.7)	
Kidney function			
eGFR (>= 60ml/min)	297 (18.8)	97 (21)	0.31
eGFR (< 60ml/min)	1281 (77.8)	366 (22.2)	
Charlson comorbidity index score			
0	788 (42.3)	246 (45.5)	0.41
1	498 (26.7)	135 (25.0)	
>1	579 (31)	160 (29.6)	
N of prescriptions during the EP			
1-3	701 (37.4)	247 (46.6)	**0.000**
4-6	686 (36.6)	180 (34.0)	
≥7	489 (26.1)	17.4 (19.4)	
Antihypertensive drug			
CCB	454 (24.3)	158 (29.2)	**0.039**
BB	277 (14.9)	84 (15.5)	
ACEI	549 (29.4)	127 (21.5)	
ARB	329 (17.6)	103 (19)	
TZD	256 (13.7)	69 (12.8)	

ACEI, Angiotensin converting enzyme inhibitor; AD, antidepressants medication; ARBs, Angiotensin II receptor blockers; BB, β-blockers; BMI, body mass index; CCB, calcium channel clocker; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; EP, exposure period; N, number SBP, systolic blood pressure; TZD, thiazide diuretics. X2 test and T-test were used for continuous and categorical data respectively. Continuous data are presented in mean (M)/ slandered deviation (SD), Categorical data are presented in numbers (%).

7.4.1.4 **Antihypertensive monotherapy and incidence of depression**

During a median of 4.4 (interquartile range 2.6–6.0) years of follow-up, there were 541 incident depression events. The overall incidence rate of depression was 52 per 1000 person-years among patients treated with antihypertensive monotherapy during the exposure period (Table 7-4). The crude depression rate per 1000 person-years was significantly higher among participants who received CCB (62.7 per 1000 persons-years) compared to the rates in the other four groups—i.e. ACEI, ARB, BB and TZD (Table 7-4).

Figure 7-4 shows the Kaplan Meir plot for incident depression comparing the major five classes of antihypertensive drugs. The difference between groups tested by the log rank test was statistically significant (p=0.002). None of the groups reached median survival probabilities during the follow-up period, but as is evident from Figure 7-4, ARB and CCB show higher risk of incident depression compared to other groups.

Table 7-4 presents the associations between the antihypertensive medication classes and subsequent depression events using multivariable Cox regression analysis. After adjustment for age and gender in model 1, CCB showed significant higher risk (HR = 1.42, 95% CI 1.13–1.81, p = 0.004) compared with the reference group (i.e. ACEI). Model 2 was adjusted for additional covariates (BMI, smoking, cholesterol, eGFR and CCI); the direct association between CCB and depression persisted with a slight attenuation of the risk magnitude (HR = 1.38, 95% CI 1.07–1.80, p = 0.014). The point estimates for the other antihypertensive groups were greater than 1 but the confidence intervals overlapped 1 and thus were not significantly different to the ACEI group.

As expected, females were at higher risk of developing depression compared to males (HR = 1.50, 95% CI 1.24–1.82, p < 0.000). Both smoking and BMI were significantly associated with depression, with HRs of 1.34 (95% CI 1.11–1.61, p = 0.002) and 1.02 (95% CI 1.01–1.04, p = 0.004), respectively. An increasing number of prescriptions was associated with a lower risk of incident depression; however, non-statistically significant (HR=0.98 95%CI 0.91, 1.07).

7.4.1.5 Sensitivity analysis

To test the robustness of my findings, I repeated the analyses excluding the depression events that occurred within the first year of follow-up (Table 7-5). The results remained stable, showing a direct association between CCB and depression (HR =1.38, 95% CI 1.03–1.85). After restricting the analysis to include participants with a minimum of 3 prescriptions of antihypertensive medication during the exposure period, both CCB (HR =1.45 95%CI 1.05, 1.98; P-value= 0.02) and ARB (HR=1.42, 95%CI 1.01,1.99 *p*= 0.04) were significantly associated with incident depression in the fully adjusted model.

The association between CCB and incident depression (HR = 1.45, 95% CI 1.06–1.95, *p* = 0.02) persisted after I excluded patients with prevalent CVD and those who developed CVD within the 12 months of the exposure period (Table 7-5).

Additionally, I used a strict criterion to define depression cases: the patients should have been on antidepressant therapy for at least six months within the first 12 months since the index date prescription (Kennedy et al., 2016). The patterns of association were similar to those of the primary analysis, showing that CCB is a strong predictor of incident depression. The magnitude of the HR increases (HR = 1.63, 95% CI 1.01–2.63, *p* = 0.047) which may be due to decreased events number and therefore reduced precision of the magnitude. (Table 7-5).

Finally, I manually censored all patients survival time at 3.5 years, which is around the average period of the follow-up in the present study. This analysis was performed as patients were more likely to discontue medication with longer time of follow-up. The relationship between CCB and incident hyperension remained unchanged (HR= 1.39 95%CI 1.02, 1.91) (Table 7-5).

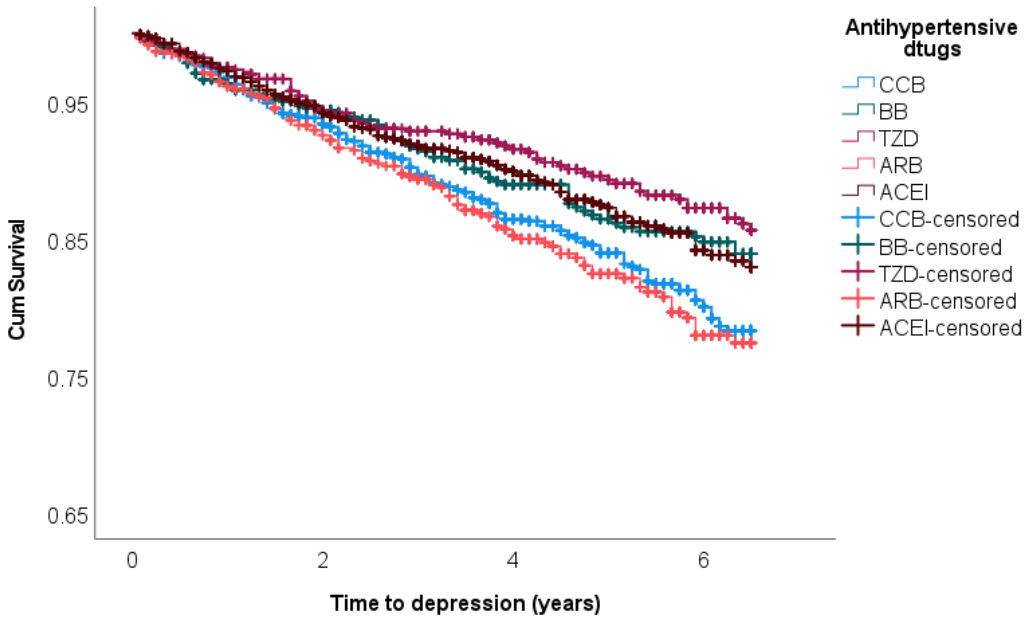

Figure 7-4 Unadjusted Kaplan Meier curves for onset of depression as indicated by receipt of antidepressants prescriptions, by antihypertensive classes in hypertensive patients newly treated with antihypertensive medication within first 12 months window
*Patients censored at 6.5 years

Table 7-4 Cox PH model results for risk of depression and different antihypertensive medication classes among patients on antihypertensive monotherapy

	Events/Total (%)	Incident rate per 1000 person-year	Univarite		Model 1		Model 2	
			HR (95%CI)	*p*-value	HR (95%CI)	*p*-value	HR (95%CI)	*p*-value
Antihypertensive class								
ACEI	128/676 (18.93)	45	**Ref (1)**		**Ref (1)**		**Ref (1)**	
ARB	103/432 (23.84)	53.6	1.39 (1.07, 1.82)	**0.01**	1.22 (0.94,1.58)	0.14	1.24 (0.93,1.01)	0.13
BB	84/361 (23.26)	53.3	0.99 (0.75, 1.32)	0.98	1.15 (0.87,1.52)	0.33	1.17 (0.86,1.59)	0.31
CCB	158/612 (25.82)	62.71	1.30 (1.03, 1.65)	**0.027**	1.42 (1.13,1.81)	**0.003**	1.38 (1.07,1.80)	**0.014**
TZD	69/325 (21.23)	44.12	0.83 (0.62, 1.12)	0.23	0.97 (0.72,1.31)	0.83	1.05 (0.76,1.44)	0.75
Total	541/2406 (22.5)	52						
Variables								
Age			0.998 (0.992, 1.004)	0.43	0.99 (0.98,1.00)	0.13	0.99 (0.98,1.01)	0.82
Female			1.49 (1.25, 1.77)	**0.00**	1.52 (1.28,1.81)	**0.000**	1.50 (1.24,1.82)	**0.000**
BMI			1.02 (1.01, 1.04)	**0.003**	1.02 (1.01,1.04)	**0.002**	1.02 (1.01,1.04)	**0.004**
Smoking			1.23 (1.03, 1.45)	**0.022**	1.25 (1.05,1.49)	**0.01**	1.34 (1.11,1.61)	**0.002**
eGFR			0.86 (0.68, 1.08)	0.19	0.85 (0.66,1.08)	0.18	0.84 (0.65, 1.07)	0.17
Cholesterol			1.03 (0.96, 1.12)	0.34	1.03 (0.95,1.11)	0.39	1.02 (0.94, 1.10)	0.62
CCI			0.94 (0.85, 1.05)	0.29	0.86 (0.68,1.00)	0.23	0.88 (0.68,1.14)	0.33
N of prescription during the EP			0.97 (0.89, 1.05)	0.45	0.97 (0.91, 1.05)	0.58	0.98 (0.91, 1.07)	0.75

Model 1 adjusted for age and gender. Model 2 adjusted for age, gender, BMI, smoking, eGFR, cholesterol and Charlson comorbidity index. Abbreviations: ACEI, Angiotensin converting enzyme inhibitor; ARB, Angiotensin II receptor blockers; BB, β-blockers; BMI, body mass index; CCB, calcium channel clocker; CI, confidence interval; EP; exposure period; N, number; HR, hazard ratio; TZD, thiazide diuretics.

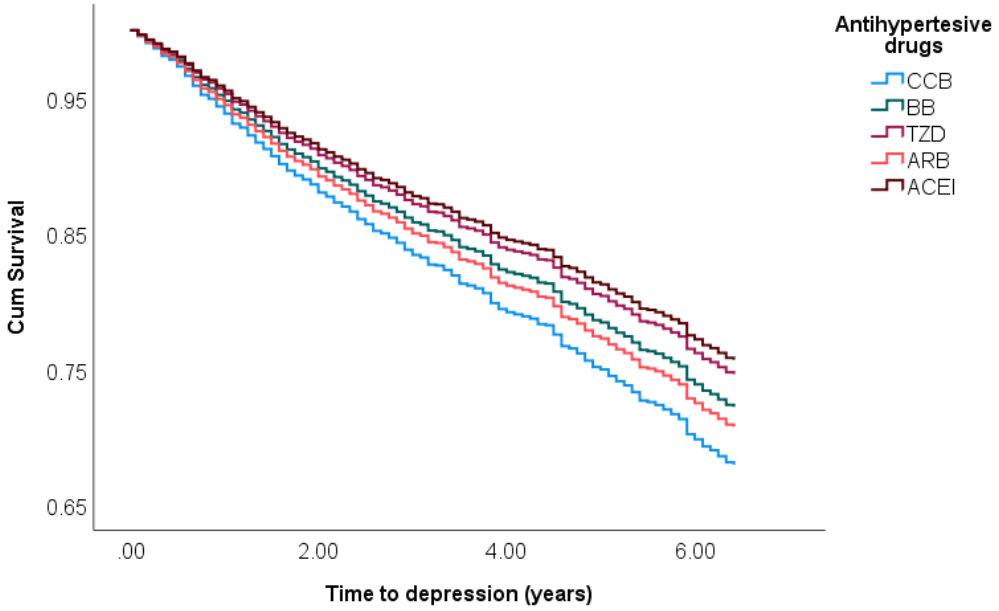

Figure 7-5 Adjusted survival plot for onset of depression as indicated by receipt of antidepressants prescriptions, by antihypertensive classes in hypertensive patients newly treated with antihypertensive medication within first 12 months window

This figure shows greatest hazard for patients treated with CCB compared with those patients with ACEI Abbreviations: ACEI, Angiotensin converting enzyme inhibitor; ARBs, Angiotensin II receptor blockers; BB, β-blockers;; CCB, calcium channel clocker

Table 7-5 Cox PH model results for risk of depression and different antihypertensive medication classes (sensitivity analysis)

		Model 1		Model 2	
	Events/Total (%)	HR (95%CI)	*p*-value	HR (95%CI)	*p*-value
Excluding cases occurring within the first year of follow-up (N= 2282)					
ACEI	95/647	**Ref (1)**		**Ref (1)**	
ARB	79/409	1.20 (0.89,1.61)	0.23	1.17 (0.85,1.62)	0.32
BB	55/336	1.01 (0.73,1.41)	0.93	0.99 (0.69,1.44)	0.99
CCB	125/580	1.47 (1.12,1.92)	**0.005**	1.38 (1.03,1.85)	**0.03**
TZD	52/310	0.94 (0.66,1.32)	0.71	0.99 (0.69,1.42)	0.96
Excluding patients with antihypertesive presctreption of less than 3 months (N= 1757)					
ACEI	83/498	**Ref (1)**		**Ref (1)**	
ARB	79/323	1.39 (1.02,1.89)	**0.03**	1.42 (1.01,1.99)	**0.04**
BB	49/266	1.04 (0.73,1.49)	0.82	1.08 (0.73,1.61)	0.68
CCB	108/457	1.46 (1.09,1.94)	**0.01**	1.45 (1.05,1.98)	**0.02**
TZD	44/213	1.05 (0.72,1.52)	0.79	1.16 (0.78,1.73)	0.45
Excluding patients with CVD before and during the exposure period (N= 1950)					
ACEI	93/547	**Ref (1)**		**Ref (1)**	
ARB	85/368	1.26 (0.94,1.70)	0.12	1.33 (0.96,1.83)	0.08
BB	62/265	1.23 (0.89,1.70)	0.20	1.27 (0.89,1.82)	0.19
CCB	126/504	1.48 (1.13,1.94)	**0.004**	1.45 (1.06,1.95)	**0.017**
TZD	54/266	1.02 (0.73,1.43)	0.91	1.11 (0.77,1.61)	0.56
Outcome defined as receiving antidepressants for 6 months or more within 12 months window of the index date* (N=2406)					
ACEI	35/676	**Ref (1)**		**Ref (1)**	
ARB	19/432	0.83 (0.47,1.46)	0.52	0.87 (0.477,1.58)	0.65
BB	22/361	1.15 (0.67,1.96)	0.61	1.35 (0.77,2.37)	0.29
CCB	50/612	1.68 (1.08,2.59)	**0.02**	1.63 (1.01,2.63)	**0.047**
TZD	18/325	0.98 (0.55,1.73)	0.94	1.08 (0.58,1.97)	0.81
Patients right censored at 3.5 years censoring point (N=2406)					
ACEI	87/676	**Ref (1)**		**Ref (1)**	
ARB	71/432	1.26 (0.93, 1.74)	0.14	1.26 (0.89,1.78)	0.18
BB	59/361	1.29 (0.92, 1.78)	0.15	1.31 (0.92,1.88)	0.13
CCB	105/612	1.39 (1.04, 1.85)	**0.024**	1.39 (1.02, 1.91)	**0.037**
TZD	43/325	1.00 (0.69, 1.45)	0.98	1.08 (0.73,1.59)	0.69

Model 1 adjusted for age and gender. Model 2 adjusted for age, gender, BMI, smoking, eGFR and Charlson comorbidity index. Abbreviations: ACEI, Angiotensin converting enzyme inhibitor; ARBs, Angiotensin II receptor blockers; BB, β-blockers; BMI, body mass index; CCB, calcium channel clocker; CI, confidence interval; HR, hazard ratio., TZD; thiazide diuretics. *Patients considered having the outcome if they received antidepressants prescriptions for at least 6 months within the first 12-month window starting from the incident date of depression.

7.4.2 Dose-response relationship

7.4.2.1 CCB and risk of anti-depressants usage: subgroup analysis

Table 7-6 presents the baseline characteristics for patients treated with CCB stratified based on whether or not they developed depression. Over a median of 4.1 years of follow-up, 158 (25.8%) of these patients developed depression. Generally, there were no major differences between the two groups ($p > 0.05$); however, patients with depression were more likely to be female ($p < 0.000$). The cDDD also varied significantly between the two groups ($p = 0.02$).

The baseline characteristics were further stratified according to the cDDD tertiles (Table 7-7). There were no differences between the groups except for gender and number of prescreption. The female proportion was higher in the first tertile compared to the second and third ones ($p = 0.03$). The patients in the first and second tertiles were more likely to be short-term users (i.e. used CCB for less than or equal to 6 months) ($p < 0.000$).

From the Kaplan-Meier survival curve in Figure 7-6, it is clear that there are no significant differences in the estimated mean event-free survival times between the three tertiles of the cDDD of CCB. The log-rank test shows a *p*-value of 0.66. The adjusted survival plot for depression incidence stratified based on the cDDD tertiles of CCB are presented in Figure 7-7.

Table 7-8 shows the Cox regression for incident depression across the cDDD tertiles of CCB. After adjusting for age and gender in Model 1, the patients in the second and third tertiles were not at increased risk of developing depression compared to those in the first tertile. The corresponding HRs are 0.93 (95% CI 0.63–1.36) and 0.91 (95% CI 0.63–1.36). Similar results were obtained after adjusting for smoking in Model 2. The corresponding HRs for the second and third tertiles are 0.93 (95% CI 0.63–1.36) and 0.91 (95% CI 0.60–1.37).

Table 7-6 Baseline characteristics of 612 patients on CCB monotherapy stratified by the main outcome

Variable	No depression N=454 (74.2)	New-onset depression N=158 (25.8)	*p*-value
Age (years)	52.66 (13.74)	52.44 (13.62)	0.86
SBP, mmHg	160.23 (25.8)	158.71 (23.14)	0.515
DBP, mmHg	94.90 (13.15)	92.72 (13.3)	0..075
Cholesterol	5.81 (1.15)	5.83 (1.07)	0.85
BMI	28.20 (4.79)	28.86 (6.5)	0.25
Gender			
Male	235 (51.58)	56 (35.4)	**0.000**
Female	219 (48.2)	102 (64.6)	
Smoking			
Non-smoker	287 (63.2)	95 (60.1)	0.49
Smoker	167 (36.8)	63 (39.9)	
Kidney function			
eGFR (>60ml/min)	78 (20.4)	30 (23.3)	0.49
eGFR (<= 60ml/min)	304 (79.6)	99 (76.7)	
Charlson comorbidity index score			
0	175 (38.5)	62 (39.2)	0.82
1	121 (26.7)	45 (28.5)	
>1	158 (34.8)	51 (32.3)	
N of prescriptions during the EP			
1-3	157 (34.5)	69 (43.9)	0.08
4-6	188 (41.3)	59 (37.6)	
≥7	110 (24.2)	29 (20.9)	
cDDD tertiles			
T1	102 (22.4)	47 (29.9)	**0.02**
T2	163 (25.8)	63 (40.1)	
T3	190 (41.8)	29.9 (19.8)	

BMI, body mass index; cDDD, cumulative defined daily dose; DBP, diastolic blood pressure; EP, exposure period; eGFR, estimated glomerular filtration rate; N, number; SBP, systolic blood pressure; T_1, first tertile; T_2, second tertile; T_3, third tertile. X^2 test and T-test were used for continuous and categorical data respectively; *p*-value for trend

Table 7-7 Baseline characteristics of 612 patients on CCB with and without depression stratified by the cDDD levels

Variable	First tertile (N= 149)	Second tertile (N= 226)	Third tertile (N=237)	*p*-value
Age (years)	54.66 (12.91)	51.86 (14.1)	52 (13.7)	0.11
Female sex	92 (61.7)	115 (50.9)	114 (48.1)	**0.03**
SBP,mmHg	159 (23.7)	157.66 (23.92)	161.80 (26.99)	0.21
DBP,mmHg	93.36 (14.27)	94.23 (13.1)	95.06 (12.62)	0.47
BMI	28.47 (5.1)	28.13 (5.4)	28.54 (5.37)	0.69
Cholesterol	5.81 (1.06)	5.75 (1.10)	5.88 (1.2)	0.50
Smoking	55 (36.9)	84 (37.2)	91 (38.4)	0.94
eGFR (< 60ml/min)	98 (79)	158 (81.9)	147 (75.8)	0.34
Charlson index score				0.62
0	50 (33.6)	88 (38.9)	99 (41.8)	
1	43 (28.9)	61 (27)	62 (26.2)	
>1	56 (37.6)	77 (34.1)	76 (32.1)	
N of prescriptions during the EP				
1-3	142 (95.3)	72 (31.9)	12 (5.1)	
4-6	7 (4.7)	123 (54.4)	117 (47.4)	**0.000**
≥7	0 (0.0)	31 (13.7)	108 (45.6)	

BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; EP, exposure period; N, number; SBP, systolic blood pressure. X^2 test and 1-way ANOVA test were used for categorical and continuous data respectively.

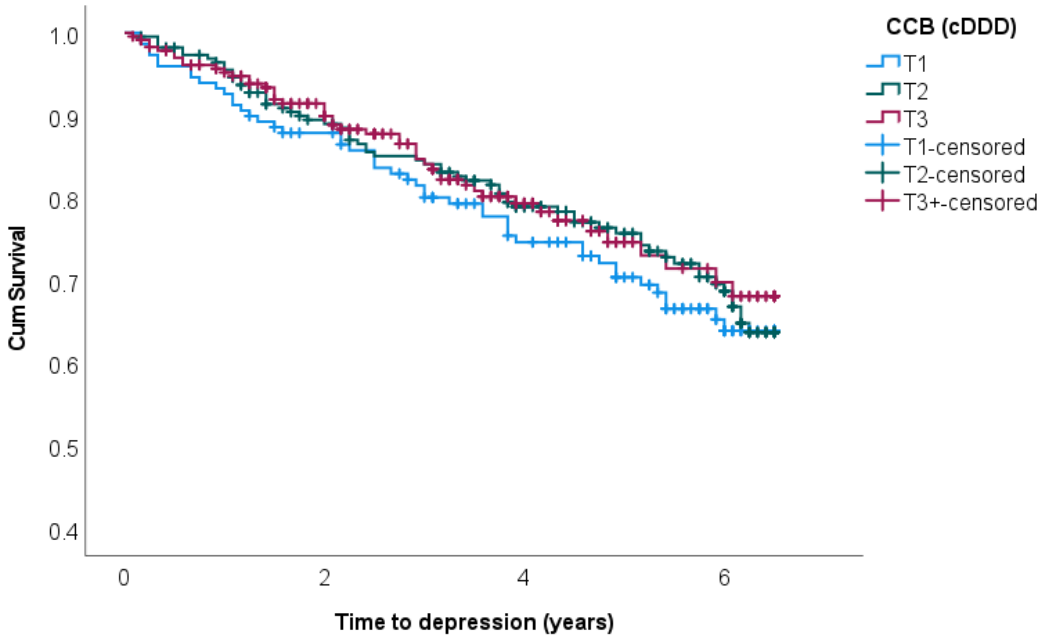

Figure 7-6 Unadjusted Kaplan Meier curves for onset of depression stratified by tertiles of the cDDD of CCB monotherapy received within the first 12 months window from the index date.
Abbrevations: CCB, calcium channel blocker; cDDD, cumulative defined daily dose; T_1, first tertile; T_2, second tertile; T_3, third tertile.

Table 7-8 Cox proportional hazards model results for risk of depression and cDDD tertiles

CCB (cDDD groups)	Events/total (%)	Incident rate per 1000 person-year	Model 1		Model 2	
			HR (95%CI)	*p*-value	HR (95%CI)	*p*-value
T_1	48/149 (32.2)	71.04	**ref (1)**		**ref (1)**	
T_2	63/226 (27.8)	61.9	0.93 (0.63, 1.36)	0.72	0.93 (0.63, 1.36)	0.72
T_3	47/237 (19.8)	56.7	0.91 (0.60, 1.37)	0.6	0.91 (0.60, 1.37)	0.64

Model 1 adjusted for age and gender. Model 2 adjusted for age, gender and smoking. Abbreviations: CCB, calcium channel blocker; CI, confidence interval; DDD; defined daily dose; HR, hazard ratio; T_1, first tertile; T_2, second tertile; T_3, third tertile.

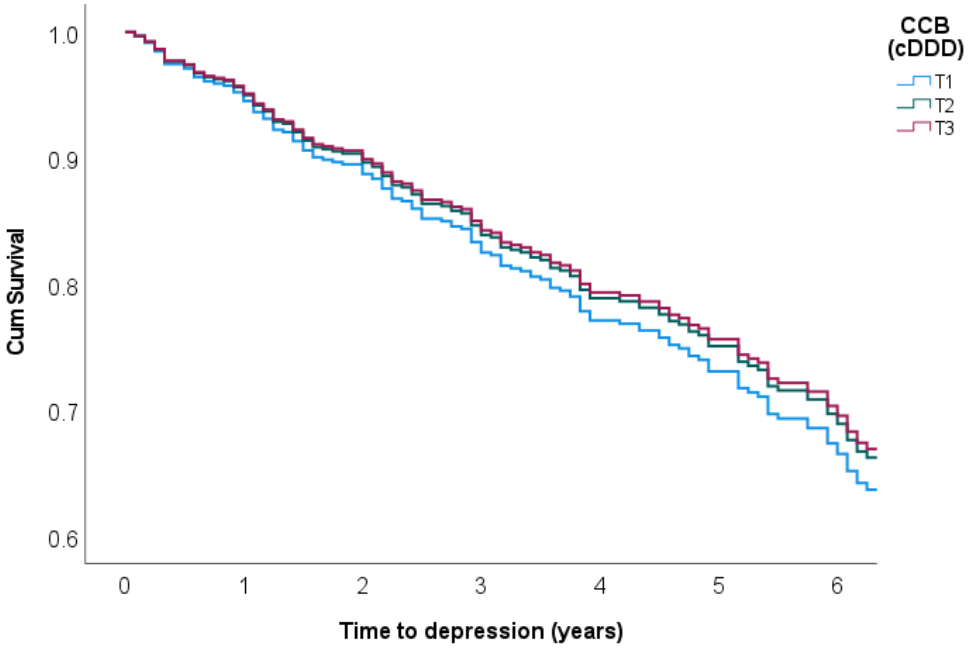

Figure 7-7 Adjusted survival plot for onset of depression stratified by tertiles of the cDDD of CCB monotherapy received within the first 12 months window of the treatment
This figure shows no difference in risk between the three groups. Abbreviations: CCB, calcium channel clocker; cDDD; cumulative defined daily dose; T_1, first tertile; T_2 second tertile; T_3 third tertile.

7.4.2.2 BB and risk of depression: subgroup analysis

The characteristics of 361 patients treated with BB stratified based on whether they developed depression or not are presented in Table 7-9. Over a median of 4.5 years of follow-up, 84 (23.3%) of these patients developed depression. These subjects were mainly female (p = 0.007), younger (p = 0.001), short-term users of BB (treated for less than or equal to 6 months) (p = 0.023) and had a lower burden of comorbidities at baseline (p = 0.005) compared to those who did not develop depression.

The baseline characteristics of patients treated with BB stratified by the cDDD tertiles are presented in Table 7-10. Comparing the three groups, the patients in the first tertile were predominantly female (≈78%). The number of prescriptions varied considerably between the groups, with those in the higher tertile being more likely to be long-term users.

Figure 7-8 displays the unadjusted Kaplan–Meier event-free survival curve, showing that the estimated mean event free-survival time is longer for the third tertile compared to the first tertile, although with borderline significance as indicated by the log-rank test (p = 0.05).

Figure 7-9 shows the adjusted survival plot for depression incidence stratified based on the cDDD tertiles of BB. The corresponding associations calculated using the Cox model are displayed in Table 7-11. Model 1 was adjusted for age and gender, while Model 2 was additionally adjusted for BMI and CCI score. In Model 1, there was no apparent difference in the risk of depression incidence between patients in the second cDDD tertile compared to those in the first tertile (HR = 0.72, 95% CI 0.42–1.26, p = 0.26). The association between the second tertile of cDDD and depression incidence remained unchanged in Model 2 (HR = 0.70, 95% CI 0.39–1.23, p = 0.21). On the other hand, the patients in the third tertile appeared to be at lower risk of developing depression compared to the first tertile, although this was not significant in the age-gender adjusted model (HR = 0.62, 95% CI 0.35–1.09, p = 0.09). Similar to the results of the log-rank test, the relationship between the third tertile and depression incidence became marginally significant as the BMI and CCI covariates were added into the model (HR = 0.6, 95% CI 0.34–1.06, p = 0.08).

Table 7-9 Baseline characteristics of 361 patients on BB monotherapy stratified by the main outcome

Variable	No depression N= 277 (76.7)	Depressed N=84 (23.3)	*p*-value
Age (years)	51.83 (13.99)	46.04 (14.94)	**0.001**
SBP, mmHg	154.32 (23.9)	152.36 (24.06)	0.52
DBP, mmHg	92.44 (12.115)	92.49 (13.88)	0.97
Cholesterol	5.7 (0.99)	5.61 (1.02)	0.47
BMI	28.52 (5.52)	29.04 (6.95)	0.48
Gender			
Male	139 (50.2)	28 (33.3)	**0.007**
Female	138 (49.8)	56 (66.7)	
Smoking			
Non-smoker	173 (62.5)	50 (59.5)	0.63
Smoker	104 (37.5)	34 (40.5)	
Kidney function			
eGFR (≥60ml/min)	47 (19.9)	10 (14.1)	0.27
eGFR (<60ml/min)	189 (80.1)	61 (85.9)	
Charlson comorbidity index score			
0	106 (38.3)	49 (58.3)	
1	84 (30)	17 (20.2)	**0.005**
>1	87 (31.4)	18 (21.4)	
N of prescriptions during the EP			
1-3	100 (35.6)	41 (51.2)	
4-6	88 (31.3)	23 (28.7)	**0.02**
≥7	93 (33.1)	16 (20.0)	
cDDD tertiles			
T1	44 (15.7)	24 (30.0)	
T2	103 (78)	29 (22)	**0.009**
T3	134 (47.7)	27 (33.8)	

BMI, body mass index; cDDD, cumulative defined daily dose; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; EP, exposure period; N, number; SBP, systolic blood pressure; T_1, first tertile; T_2, second tertile; T_3, third tertile. X2 test and T-test were used

Table 7-10 Baseline characteristics of 361 patients on BB monotherapy stratified by cDDD levels

Variable	First tertile N=68 (18.8)	Second tertile N=132 (36.6)	Third tertile N=161 (44.6)	*p*-value
Age (years)	48.24 (15.2)	51.02 (14.8)	50.99 (13.65)	0.36
Female sex	53 (77.9)	64 (48.5)	77 (47.8)	**0.000**
SBP,mmHg	151.24 (21.8)	152.32 (24.84)	156.27 (24.04)	0.23
DBP,mmHg	93.23 (11.5)	91.7 (13.3)	92.73 (12.2)	0.66
BMI	27.8 (5.57)	29.02 (6.43)	28.69 (5.51)	0.37
Smoking	26 (39.2)	55 (41.7)	57 (35.4)	0.55
Cholesterol	5.7 (1.07)	5.62 (1.04)	5.7 (0.92)	0.65
eGFR (< 60ml/min)	43 (75.4)	91 (84.3)	116 (81.7)	0.38
Charlson index score				
0	33 (48.5)	53 (40.2)	69 (42.9)	0.18
1	22 (32.4)	32 (24.2)	47 (29.2)	
>1	13 (19.1)	47 (35.6)	45 (28.0)	
N of prescriptions during the EP				
1-3	60 (88%)	64 (48.5)	17 (10.6)	**0.000**
4-6	6 (8.8)	40 (30.3)	65 (40.4)	
≥7	2 (2.9)	28 (21.2)	79 (49.1)	

BMI, body mass index; cDDD, cumulative defined daily dose; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; EP, exposure period; N, number; SBP, systolic blood pressure. X^2 test and 1-way ANOVA test were used for categorical and continues data respectively.

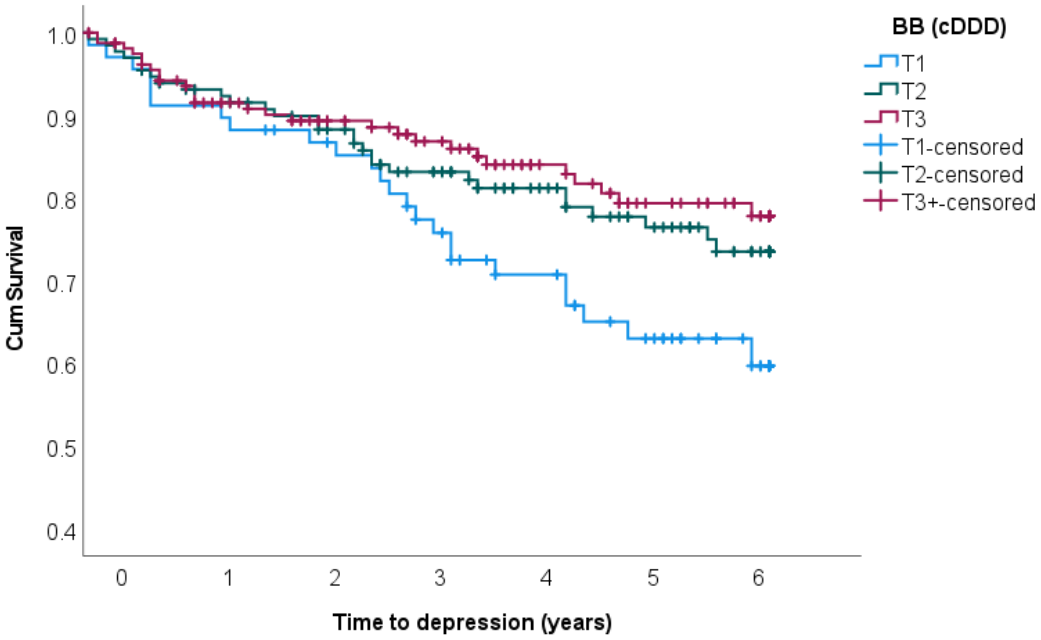

Figure 7-8 Unadjusted Kaplan Meier curves for onset of depression stratified by tertiles of the cDDD of BB monotherapy received within the first 12 months window from the BB prescription index date.
BB, beta-blocker; cDDD, cumulative defined daily dose; T_1, first tertile; T_2, second tertile; T_3, third tertile

Table 7-11 Cox PH model results for risk of depression and different cDDD levels of BB

BB (cDDD groups)	Events/total (%)	Incident rate per 1000 person-year	Model 1		Model 2	
			HR (95%CI)	*p*-value	HR (95%CI)	*p*-value
T_1	25/68 (36.7)	**82**	**ref (1)**		**ref (1)**	
T_2	31/132 (23.5)	51.4	0.72 (0.42, 1.26)	0.26	0.70 (0.39, 1.23)	0.21
T_3	28/161 (17.4)	41.9	0.62 (0.35, 1.09)	0.09	0.60 (0.34, 1.06)	0.08

Model 1 adjusted for age and gender. Model 2 adjusted for age, gender, BMI and charlson comorbidity index score. Abbreviations: BB, β-blockers; CI, confidence interval; cDDD; cumulative defined daily dose; HR, hazard ratio; T_1, first tertile; T_2, second tertile; T_3, third tertile.

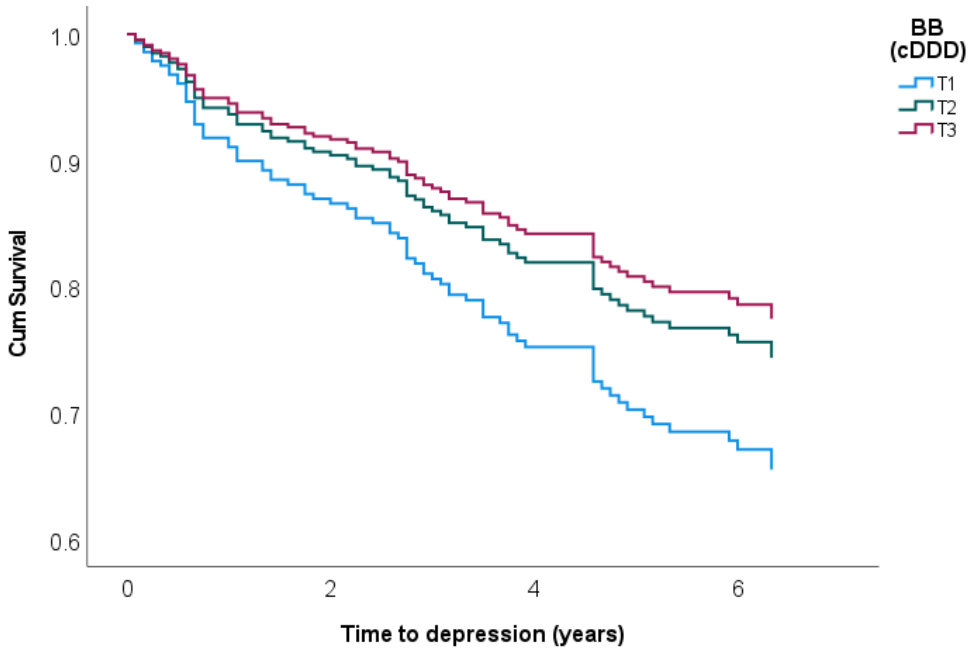

Figure 7-9 Adjusted survival plot for new-onset of depression stratified by tertiles of the cDDD of BB monotherapy received within the first 12 months window from the BB prescription index date.
This figure shows no significant differences in risk of depression incident between the three groups. Abbreviations: BB, β-blockers; cDDD; cumulative defined daily dose; T_1, first tertile; T_2 second tertile; T_3 third tertile.

7.4.2.3 ACEI and risk of depression: subgroup analysis

The baseline characteristics of 676 patients treated with ACEI are shown in Table 7-12. Overall, 127 (18.8%) of these patients developed depression over a median follow-up of 4.3 years. Comparing the groups with and without depression, subjects in the group with incident depression were significantly more likely to be overweight (p = 0.003). The other characteristics were comparable between the two groups.

Table 7-13 shows the baseline characteristics stratified according to the cDDD of ACEI. There were no significant differences between the three groups except for the number of ACEI prescriptions. Patients in the first and second tertiles tended to be short-term users (six prescriptions or fewer).

The unadjusted event-free Kaplan–Meier survival curve is presented in Figure 7-10. The log-rank test shows a non-statistically significant difference (p = 0.17) in the mean event-free survival time between the three tertiles of the cDDD of ACEI.

Table 7-14 presents the association between the cDDD tertiles within the ACEI group and the risk for depression incidence. Model 1 was adjusted for age and gender, while Model 2 was further adjusted for BMI and smoking. In both models, the association between the second tertile and depression compared to the first tertile was not significant: HR = 1.08 (95% CI 0.72–1.62, p = 0.71) and HR = 1.09 (95% CI 0.73–1.63, p = 0.67), respectively. On the other hand, the patients in the third tertile appeared to be at lower risk of incident depression compared to those in the first tertile, although this association was not statistically significant in either models (Model 1: HR = 0.68, 95% CI 0.42–1.09, p = 0.11; Model 2: HR = 0.69, 95% CI 0.43–1.11, p = 0.12) (Figure 7-11).

Table 7-12 Baseline characteristics of 676 patients on ACEI monotherapy stratified by the main outcome

Variable	No depression N= 549 (81.2)	Depressed N= 127 (18.8)	*p*-value
Age (years)	48.63 (14.55)	49.17 (13.12)	0.71
SBP	154.95 (23.43)	153.19 (26.18)	0.46
DBP	92.97 (12.08)	92.16 (11.45)	0.49
Cholesterol	5.7 (1.11)	5.88 (1.15)	0.29
BMI	27.8 (4.96)	29.54 (6.05)	**0.003**
Gender			
Male	298 (54.3)	64 (50.4)	0.43
Female	251 (45.7)	63 (49.6)	
Smoking			
Non-smoker	359 (65.4)	73 (57.5)	0.09
Smoker	190 (34.6)	54 (42.5)	
Kidney function			
eGFR (>60ml/min)	73 (16.2)	21 (19.6)	0.39
eGFR (<= 60ml/min)	377 (83.8)	86 (80.4)	
Charlson comorbidity index score			
0	279 (50.8)	66 (52.0)	0.76
1	124 (22.6)	25 (19.7)	
>1	146 (26.6)	36 (28.3)	
N of prescriptions during the EP			
1-3	124 (48.1)	34 (50.7)	0.86
4-6	93 (36.0)	24 (20.5)	
≥7	41 (15.9)	9 (13.4)	
cDDD tertiles			
T1	147 (26.6)	43 (34.7)	**0.008**
T2	196 (35.3)	52 (41.9)	
T3	210 (28)	29 (23.4)	

BMI, body mass index; cDDD, cumulative defined daily dose; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; EP, exposure perioed; N, number; SBP, systolic blood pressure; T_1, first tertile; T_2, second tertile; T_3, third tertile. X^2 test and T-test were used for categorical and continuous data respectively

Table 7-13 Baseline characteristics of 681 patients on ACEI monotherapy stratified by cDDD tertiles

Variable	First tertile N=190 (28.1)	Second tertile N=247 (36.5)	Third tertile N=239 (35.4)	*p*-value
Age (years)	48.20 (15.04)	49.68 (13.99)	46.39 (13.97)	0.42
Female sex	91 (47.9)	111 (44.9)	112 (46.9)	0.81
SBP,mmHg	154.42 (25.46)	152.84 (22.58)	156.61 (24.08)	0.23
DBP,mmHg	93.13 (11.79)	91.63 (11.95)	93..81 (12.04)	0.12
BMI	28.4 (5.48)	28.18 (4.9)	27.85 (5.3)	0.55
Smoking	70 (36.8)	87 (35.2)	87 (36.4)	0.93
Choleserol				
eGFR (< 60ml/min)	131 (82.9)	166 (82.2)	166 (84.3)	0.85
Charlson index score				
0	101 (53.2)	123 (49.8)	121 (50.6)	
1	36 (18.9)	54 (21.9)	59 (24.7)	
>1	53 (27.9)	70 (28.3)	59 (24.7)	0.63
N of prescriptions during the EP				
1-3	155 (81.6)	79 (32)	23 (8.9)	
4-6	29 (15.3)	95 (39.5)	108 (45.2)	**0.000**
≥7	6 (3.2)	73(29.6)	108 (57.8)	

BMI, body mass index; cDDD; cumulative defined daily dose; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; EP, exposure period; N, number; SBP, systolic blood pressure. X^2 test and 1-way ANOVA test were used for categorical and continues data respectively.

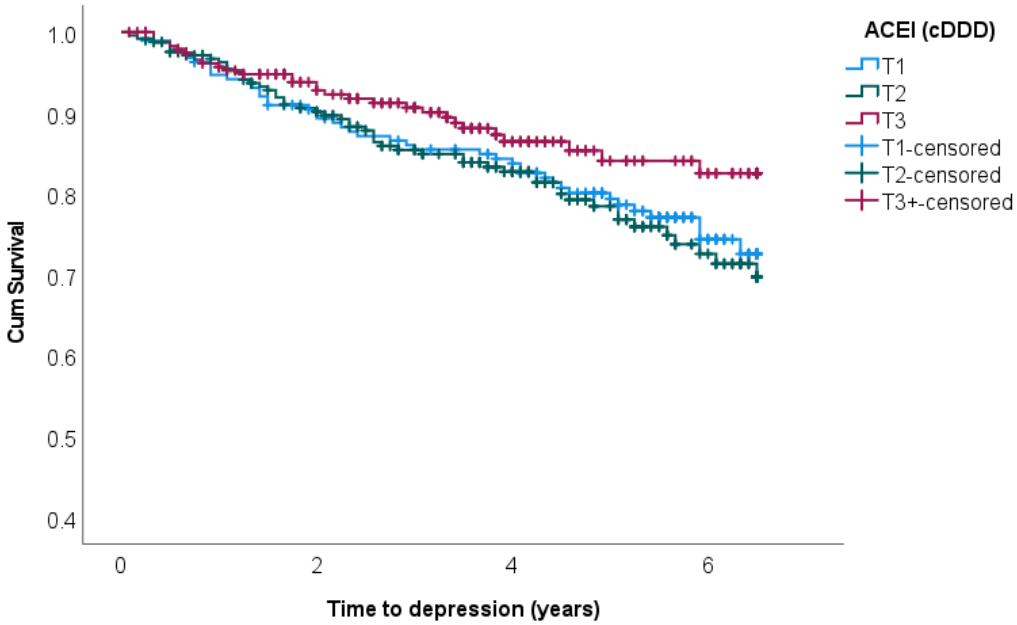

Figure 7-10 Unadjusted Kaplan Meier curves for onset of depression stratified by tertiles of the cDDD of ACEI monotherapy received within the first 12 months window from the index date.

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; cDDD, cumulative defined daily dose; T_1, first tertile; T_2, second tertile; T_3, third tertile

Table 7-14 Cox PH model results for risk of depression and different cDDD levels of ACEI

ACEI (cDDD groups)	Events/total (%)	Incident rate per 1000 person-year	Model 1		Model 2	
			HR (95%CI)	*p*-value	HR (95%CI)	*p*-value
T_1	46/190 (24.21)	50.3	**ref (1)**		**ref (1)**	
T_2	52/247 (21.1)	50.9	1.08 (0.72,1.62)	0.71	1.09 (0.73, 1.63)	0.67
T_3	29/239 (12.1)	31.9	0.68 (0.42, 1.09)	0.11	0.69 (0.43, 1.11)	0.12

Model 1 adjusted for age and gender. Model 2 adjusted for age, gender, smoking and body mass index.Abbreviations: ACEI, Angiotensin converting enzyme inhibitor; CI, confidence interval; cDDD; cumulative defined daily dose; HR, hazard ratio; T_1, first tertile; T_2, second tertile; T_3, third tertile.

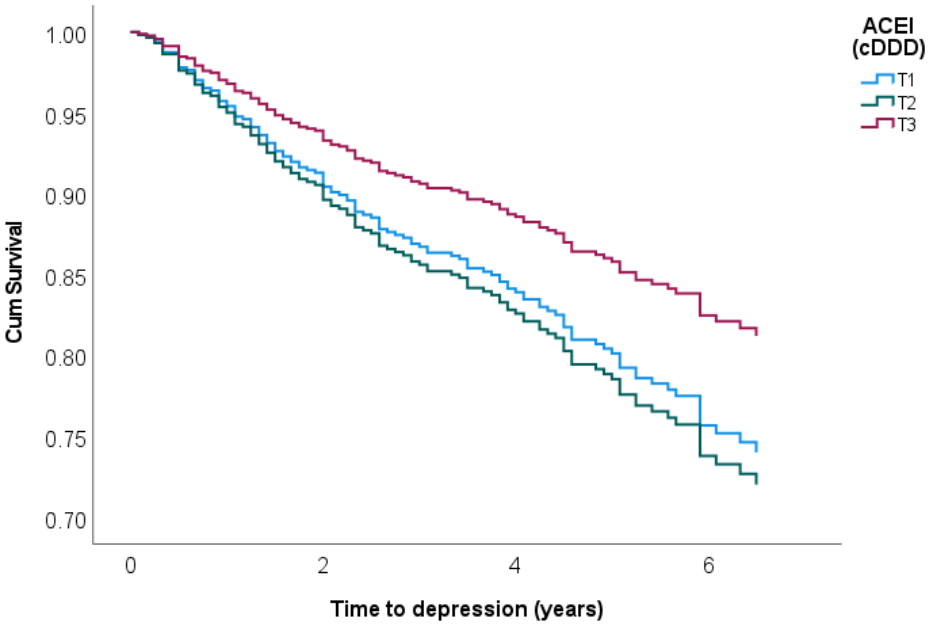

Figure 7-11 Adjusted survival plot for onset of depression stratified by tertiles of the cDDD of ACEI monotherapy received within the first 12 months window from the ACEI prescription index date.

This figure shows that patients in the third tertile were at lower risk for onset of depression compared to patients in the lower tertile, though the association was marginally Abbreviations: ACEI, Angiotensin converting enzyme inhibitor; cDDD; cumulative defined daily dose; T_1, first tertile; T_2 second tertile; T_3 third tertile.

7.4.2.4 **ARB and risk of depression: subgroup analysis**

The characteristics of 432 patients treated with ARB categorised by depression outcome status are presented in Table 7-15. Over a median of 4.5 years of follow-up, 103 (23.8%) ARB-treated patients developed depression. Comparing the groups with and without depression, the patients who did develop depression were predominantly female (p = 0.003). No other significant differences between the two groups were observed.

As shown in Table 7-16, the distributions of baseline characteristics divided by the cDDD tertiles of ARB were comparable between the three groups, except for the number of prescriptions variable, as patients within the first and second tertiles were more likely to be short-term users.

The unadjusted event-free Kaplan–Meier survival curve is presented in Figure 7-12 showing a linear relationship with tertile 1 with the lowest risk and tertile 3 with higher risk but this did not reach statistical significance (log-rank p = 0.12).

Table 7-17 provides the Cox proportional hazard ratios of the association between cDDD tertile and incident depression among patients receiving ARB. Model 1 was adjusted for age and gender, whereas Model 2 was further adjusted for SBP and number of prescriptions. Using the first tertile as the reference group, the HR for the second tertile was 1.49 (95% CI 0.90–2.47, p = 0.12) and 1.43 (95% CI 0.82–2.50, p = 0.18) in Models 1 and 2, respectively. In the age-gender adjusted model, the patients in the third tertile were associated with an increased risk of developing depression (HR = 1.78, 95% CI 1.08–2.94, p = 0.02) compared to the first tertile. This association was attenuated after additional adjustments for SBP and number of prescriptions (HR = 1.77, 95% CI 0.97–3.22, p = 0.06).

Table 7-15 Baseline characteristics of 432 patients on ARB monotherapy stratified by the main outcome

Variable	No depression N= 329 (76.2)	Depressed N= 103 (23.8)	*p*-value
Age (years)	51.92 (13.46)	50.74 (13.87)	0.44
SBP	161.15 (25.41)	158.46 (23.1)	0.34
DBP	95.73 (13.10)	94.28 (11.3)	0.28
Cholesterol	5.7 (1.01)	5.87 (1.22)	0.45
BMI	28.62 (5.5)	29.15 (7.2)	0.44
Gender			
Male	180 (54.7)	39 (37.9)	**0.003**
Female	149 (45.3)	64 (62.1)	
Smoking			
Non-smoker	228 (69.3)	67 (65.0)	0.42
Smoker	101 (30.7)	36 (35.0)	
Kidney function			
eGFR (>=60ml/min)	53 (18.3)	23 (25.0)	0.16
eGFR (<60ml/min)	236 (81.7)	69 (75.0)	
Charlson comorbidity index score			
0	135 (41)	47 (45.6)	0.66
1	88 (26.7)	27 (26.2)	
>1	106 (32.2)	29 (28.2)	
N of prescriptions during the EP			
1-3	128 (38.8)	38 (37.3)	0.70
4-6	118 (35.8)	41 (40.2)	
≥7	84 (25.5)	23 (22.5)	
cDDD tertiles			
T1	102 (30.9)	26 (25.5)	0.57
T2	109 (33)	36 (24.8)	
T3	119 (36.1)	40 (39.2)	

BMI, body mass index; cDDD; cumulative defined daily dose; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; EP, exposure period; N, number; SBP, systolic blood pressure; T_1, first tertile; T_2, second tertile; T_3, third tertile. X2 test and T-test were used for categorical and continuous data respectively.

Table 7-16 Baseline characteristics of 432 patients on ARB monotherapy stratified by cDDD levels

Variable	First tertile N= 128 (29.6)	Second tertile N= 145 (33.6)	Third tertile N= 159 (36.8)	*p*-value
Age (years)	52.25 (14.36)	50.83 (13.22)	51.89 (13.24)	0.66
Female sex	70 (54.7)	74 (51.0)	69 (43.4)	0.144
SBP,mmHg	160.77 (25.5)	157.7 (26.43)	162.88 (22.6)	0.19
DBP,mmHg	95.19 (12.68)	95.08 (12.63)	95.81 (12.83)	0.87
BMI	28.61 (4.79)	29.34 (6.7)	28.31 (6.1)	0.31
Smoking	39 (30.5)	49 (33.8)	49 (30.8)	0.80
Cholesterol	5.82 (1.04)	5.8 (1.04)	5.76 (1.11)	0.86
eGFR (< 60ml/min)	94 (80.3)	95 (79.8)	116 (80.0)	0.99
Charlson index score				
0	54 (42.2)	64 (44.1)	64 (10.3)	0.61
1	29 (22.7)	38 (26.2)	48 (30.2)	
>1	45 (35.2)	43 (29.7)	47 (29.6)	
N of prescriptions during the EP				
1-3	89 (69.5)	17 (11.7)	3 (2.8)	
4-6	26 (20.3)	49 (33.8)	38 (23.9)	**0.000**
≥7	4 (3.1)	34 (23.4)	69 (43.4)	

; BMI, body mass index; cDDD; cumulative defined daily dose; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; EP, exposure period; N, number; SBP, systolic blood pressure. X^2 test and 1-way ANOVA test were used for categorical and continuous data respectively.

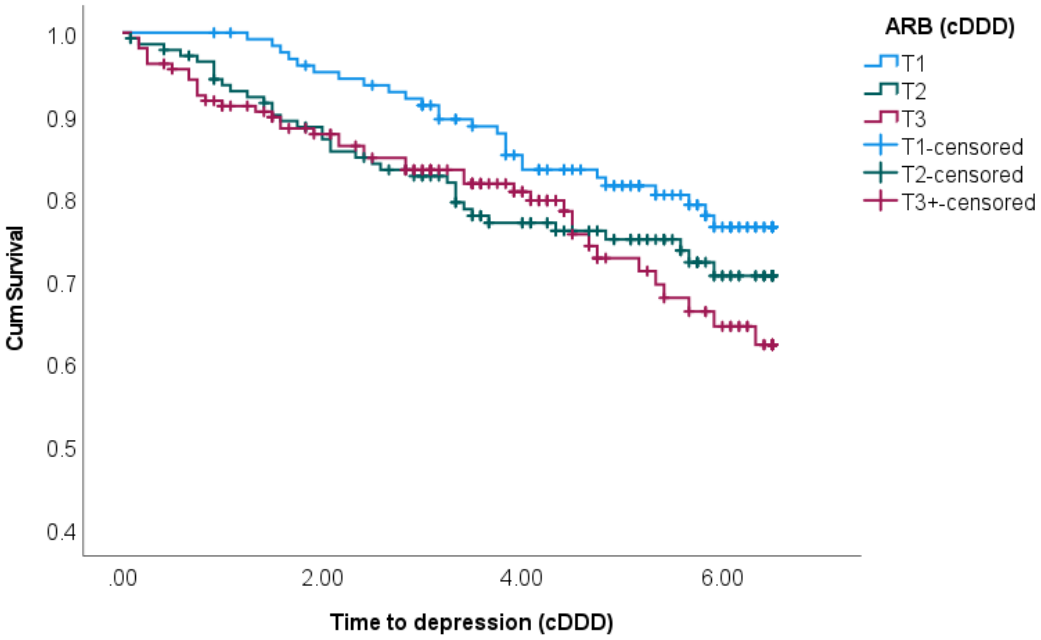

Figure 7-12 Unadjusted Kaplan Meier curves for onset of depression stratified by tertiles of the cDDD of ARB monotherapy received within the first 12 months window from the ARB prescription index date

Abbreviation: ARB, angiotensin receptor antagonist; cDDD, cumulative defined daily dose; T_1, first tertile; T_2, second tertile; T_3, third tertile

Table 7-17 Cox PH model results for risk of depression and different cDDD levels of ARB

ARB (cDDD groups)	Events/total (%)	Incident rate per 1000 person-year	Model 1		Model 2	
			HR (95%CI)	*p*-value	HR (95%CI)	*p*-value
T_1	26/128 (20.3)	39	**ref (1)**		**ref (1)**	
T_2	37/145 (25.5)	58.2	1.49 (0.90, 2.47)	0.12	1.43 (0.82, 2.50)	0.20
T_3	40/159 (25.1)	64.5	1.78 (1.08, 2.94)	**0.02**	1.77 (0.97, 3.22)	**0.06**

Model 1 adjusted for age and gender. Model 2 adjusted for age, gender, number of prescription and systolic blood pressure. Abbreviations: ARBs, Angiotensin II receptor blockers; cDDD; defined daily dose ; CI, confidence interval;; HR, hazard ratio; T_1, first tertile; T_2, second tertile; T_3, third tertile.

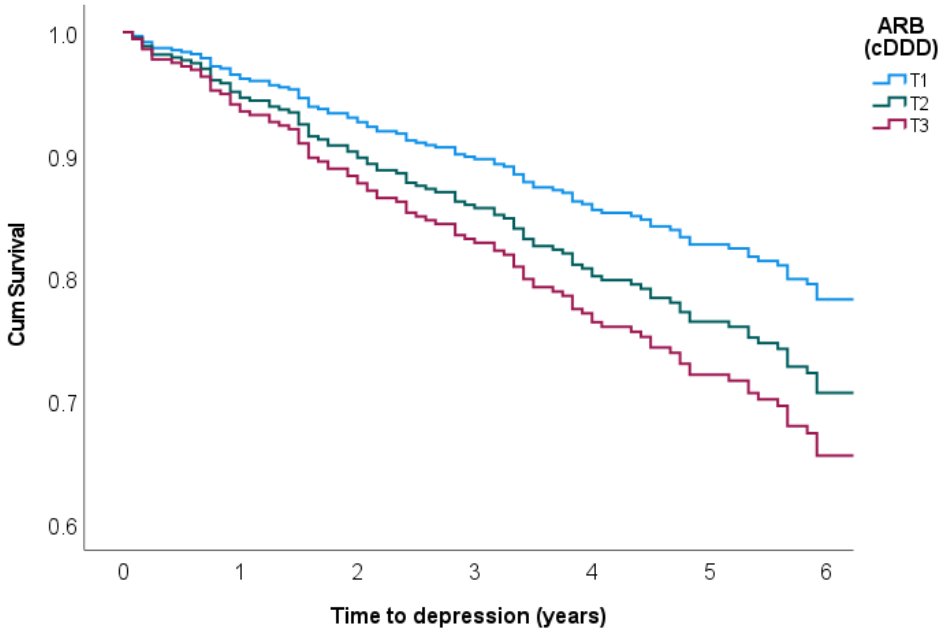

Figure 7-13 Adjusted survival plot for onset of depression as indicated by receipt of antidepressants prescriptions, by tertiles of cDDD of ARB in hypertensive patients newly treated with ARB within 12 months window.
This figure shows greatest hazard for the third tertile compared to the first tertilr of the cDDD
Abbreviations: ARBs, Angiotensin II receptor blockers; cDDD; cumulative defined daily dose; T_1, first tertile; T_2 second tertile; T_3 third tertile.

7.4.2.5 TZD and risk of depression: subgroup analysis

Table 7-18 presents the baseline characteristics for 325 patients treated with TZD, based on whether they developed depression. Sixty-nine (21.2%) cases of depression occurred over a median follow-up of 5.5 years. The participants who developed depression were predominantly female (≈61%) and had higher SBP at baseline (p = 0.02) compared to those who did not develop depression.

The baseline characteristics across the cDDD tertiles of TZD were comparable, except for the number of prescriptions, as the participants in the first and second tertiles were more often short-term users (p < 0.000) (Table 7-19).

The unadjusted event-free Kaplan-Meier survival curves (Figure 7-14) shows no significant differences in the cumulative event-free survival rate between the cDDD tertiles of TZD. The estimated mean time to depression was comparable between the three groups, as indicated by the log-rank test (p = 0.95)

Table 7-20 presents the HRs for the association between the cDDD tertiles of TZD and incidence of depression. Model 1 was adjusted for age and gender, while Model 2 was adjusted for SBP, smoking and CCI. In both models, there was no significant association between the second tertile of cDDD and risk of depression compared to the first tertile, and the HRs were almost identical (HR = 0.93 95% CI 0.50–1.73, p = 0.94). Likewise, there were no apparent differences in the risk of depression between patients in the third tertile compared to those in the first tertile. The corresponding HRs for the third tertile in Models 1 and 2 were 1.02 (95% CI 0.58–1.78, p = 0.95) and 0.98 (95% CI 0.55–1.74, p = 0.94), respectively.

Figure 7-16 displays the adjusted HRs and CI overlaps for incident depression between the tertiles of the cDDD of all five classes of antihypertensive monotherapy.

Table 7-18 Baseline characteristics of 325 patients on TZD monotherapy stratified by the main outcome

Variable	No depression N= 256 (78.8)	Depressed N= 69 (21.2)	*p*-value
Age at first prescription (years)	52.68 (13.63)	55.59 (12.5)	0.11
SBP	157.22 (22.36)	164.58 (23.24)	**0.02**
DBP	93.54 (11.11)	96.42 (13.93)	0.07
Cholesterol	5.81 (1.1)	5.7 (0.98)	0.52
BMI	28.58 (5.09)	29.12 (5.22)	0.44
Gender			
Male	115 (44.9)	27 (39.1)	0.039
Female	141 (55.1)	42 (60.9)	
Smoking			
Non-smoker	180 (70.3)	41 (59.4)	0.08
Smoker	76 (29.7)	28 (40.6)	
Kidney function			
eGFR (>= 60ml/min)	46 (20.8)	13 (20.3)	0.93
eGFR (< 60ml/min)	175 (79.2)	51 (79.7)	
Charlson comorbidity index score			
0	93 (36.3)	22 (31.9)	0.65
1	81 (31.6)	21 (30.4)	
>1	82 (32.0)	26 (37.7)	
N of prescriptions during the EP			
1-3	87 (34)	25 (36.2)	**0.001**
4-6	66 (25.8)	19 (27.5)	
≥7	41 (16)	9 (13)	
cDDD tertiles			
T1	81 (31.4)	25 (37.3)	0.59
T2	65 (25.2)	17 (25.4)	
T3	112 (43.4)	25 (37.3)	

BMI, body mass index; cDDD; cumulative defined daily dose; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; EP, exposure period; N, number; SBP, systolic blood pressure; T_1, first tertile; T_2, second tertile; T_3, third tertile. X2 test and T-test were used for categorical and continues data respectively.

Table 7-19 Baseline characteristics of 325 patients on TZD monotherapy stratified by DDD levels

Variable	First tertile N=106 (32.6)	second tertile N= 82 (25.2)	Third tertile N= 137 (42.2)	*P*-value
Age (years)	54.83 (14.28)	52.71 (13.9)	52.47 (12.3)	0.36
Female sex	60 (56.6)	52 (63.4)	71 (51.8)	0.25
SBP,mmHg	160 (21.41)	157 (22.6)	158 (23.8)	0.68
DBP,mmHg	93.14 (11.9)	93.98 (11.2)	95.03 (12.03)	0.47
BMI	28.9 (5.1)	28.67 (5.5)	28.55 (4.2)	0.87
Smoking	34 (32.1)	30 (36.6)	40 (29.2)	0.52
Choleserol	5.6 (1.1)	5.7 (1.08)	5.9 (1.03)	0.18
eGFR(< 60ml/min)	76 (79.2)	63 (84.0)	87 (76.3)	0.44
Charlson index score				0.59
0	37 (34.9)	29 (35.4)	49 (35.8)	
1	28 (26.4)	29 (35.4)	45 (32.8)	
>1	41 (38.7)	24 (29.3)	43 (31.4)	
N of prescriptions during the EP				
1-3	100 (94.3)	51 (62.2)	7 (5.1)	
4-6	6 (5.7)	27 (32.9)	84 (71.8)	**0.000**
≥7	0 (0.0)	4 (4.9)	46 (92.0)	

BMI, body mass index; cDDD; cumulative defined daily dose; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; EP, exposure period; N, number; SBP, systolic blood pressure. X^2 test and 1-way ANOVA test were used for categorical and continuous data respectively.

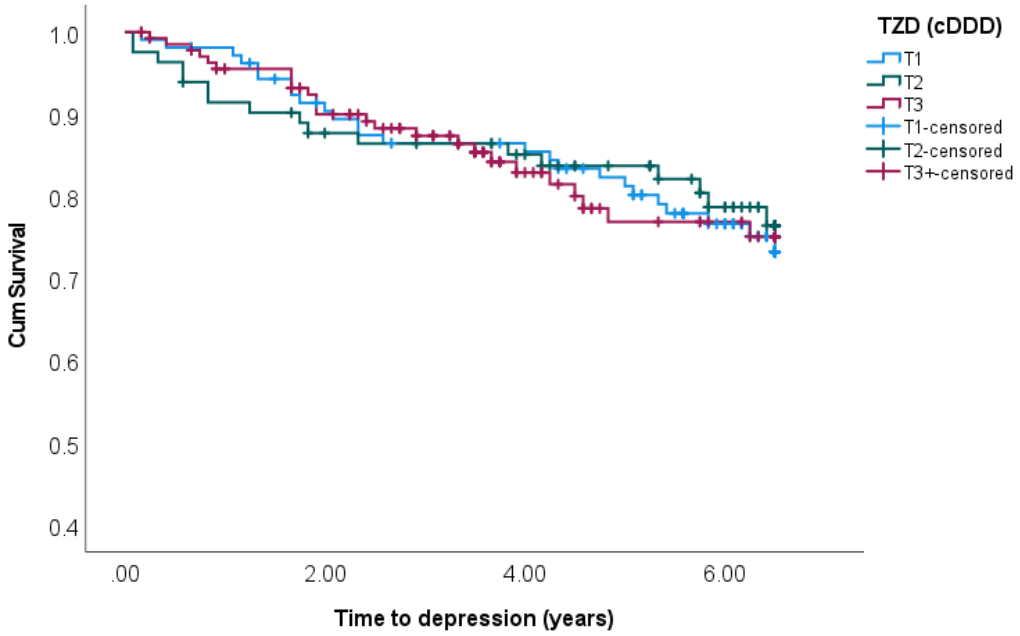

Figure 7-14 Unadjusted Kaplan Meier curves for onset of depression stratified by tertiles of the cDDD of TZD monotherapy received within the first 12 months window from the TZD prescription index date.
Abbreviation: cDDD, cumulative defined daily dose; TZD, thiazide diuretics; T_1, first tertile; T_2, second tertile; T_3, third tertile

Table 7-20 Cox PH model results for risk of depression and different cDDD levels of TZD

TZD (DDD groups)	Events/total (%)	Incident rate per 1000 person-year	Model 1		Model 2	
			HR (95%CI)	*p*-value	HR (95%CI)	*p*-value
T_1	26/106 (24.5)	45.8	**ref (1)**		**ref (1)**	
T_2	17/82 (20.7)	40	0.93 (0.50, 1.73)	0.83	0.94 (0.51, 1.74)	0.84
T_3	26/137 (18.9)	45.4	1.02 (0.58, 1.78)	0.95	0.98 (0.55, 1.74)	0.94

Model 1 adjusted for age and gender. Model 2 adjusted for age, gender, systolic blood pressure, smoking and Charlson comorbidity index score. Abbreviations: CI, confidence interval; DDD; defined daily dose; HR, hazard ratio; T_1, first tertile; T_2, second tertile; T_3, third tertile.

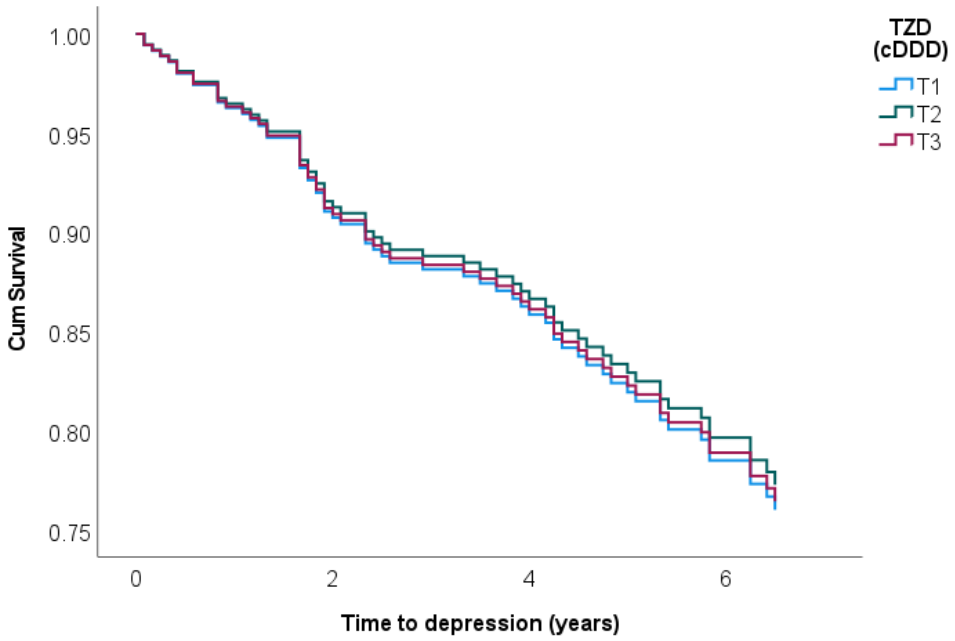

Figure 7-15 Adjusted survival plot for onset of depression as indicated by receipt of antidepressants prescriptions, by tertiles of cDDD of TZD in hypertensive patients newly treated with TZD within 12 months window.
This figure shows no significant differences between the tertiles of the cDDD of TZD. Abbreviations: cDDD; cumulative defined daily dose; TZD; thiazide diuretics; T_1, first tertile; T_2 second tertile; T_3 third tertile.

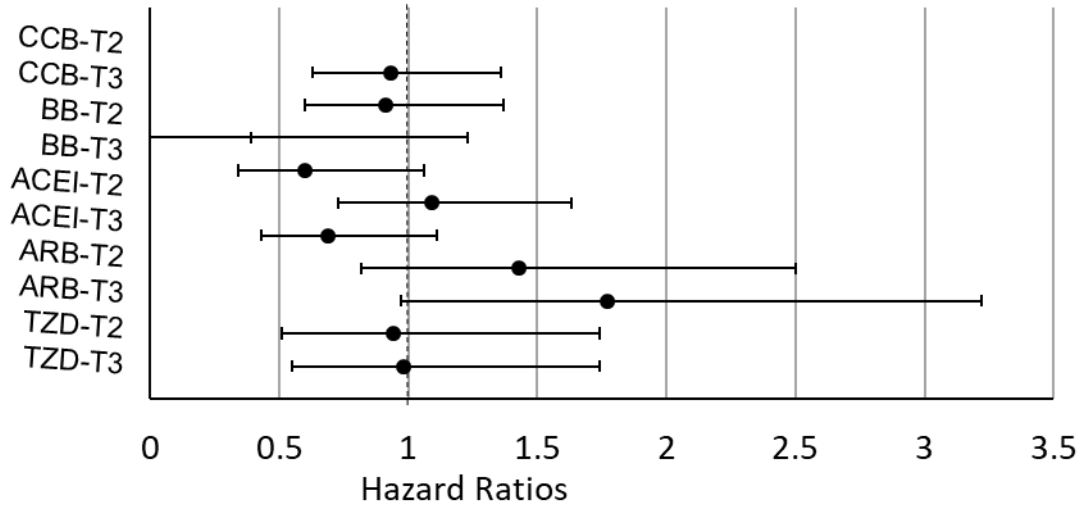

Figure 7-16 Forest plot of adjusted hazard ratios for new onset depression as indicated by receipt of antidepressants prescriptions by the cDDD tertiles of the five major classes of antihypertensive monotherapy in hypertensive

ACEI, Angiotensin converting enzyme inhibitor; ARBs, Angiotensin II receptor blockers; BB, β-blockers;CCB, calcium channel clocker; T_2, second tertile; T_3, third tertile.

7.4.3 Antihypertensive drugs and risk of depression: polytherapy analysis

7.4.3.1 General characteristics of patients on antihypertensive monotherapy or polytherapy grouped by baseline depression status and index antihypertensive drug class

Table 7-21 presents the baseline clinical characteristics of 5060 patients who were either on antihypertensive monotherapy or polytherapy, categorised based on their depression status. Patients with prevalent depression (27%) were excluded from further analysis. Compared to individuals without depression, patients with prevalent depression tend to be younger ($p < 0.00$), predominantly female ($p < 0.00$) and more likely to be smokers ($p = 0.03$) and had higher BMIs ($p = 0.00$) and lower scores of CCI at presentation ($p < 0.000$). Of the patients without depression, 14% progressed to develop new-onset depression, defined by the first-ever prescription of antidepressants. In comparison to patients with no depression, those with new-onset depression were predominantly female and more likely to be overweight and smokers.

The baseline characteristics of the 3691 eligible patients are presented in Table 7-22. They were further stratified based on the index antihypertensive drug, as presented in Table 7-23. As demonstrated, there were significant differences between drug groups in most of the baseline covariates except for cholesterol level.

7.4.4 **Quality assessment**

The overall score on the NOS is 7 (Appendix 7), which indicated a good quality of the present cohort. However, taking into account the limitation of the tool (see 2.1.5) as well as the poor guidance in the literature about the optimal measure of depression, the score may not be an accurate reflection of the study quality.

Table 7-21 Baseline characteristic of the GBPC population on antihypertensive polytherapy (N=5060) stratified based on their depression status

Variable	Depression status				
	Not depressed N=2983 (59)	**Prevalent depression N= 1369 (27.1)**	**New onset depression N=708 (14)**	***P*-value[a]**	***P*-value[b]**
Age at first prescription (years)	58.5 (13.4)	56.7 (13.2)	58.0 (13)	**0.000**	**0.42**
BMI	28.6 (5.4)	29.4 (6.4)	29.1 (6.8)	**0.000**	**0.01**
Cholesterol	5.7 (1.03)	5.79 (1.1)	5.7 (1.1)	**0.01**	**0.92**
Gender					
Male	1619 (54.3)	464 (33.9)	291 (41.1)	**0.000**	**0.000**
Female	1364 (45.7)	904 (66.1)	417 (58.9)		
Smoking					
Non-smoker	1976 (66.2)	862 (63.0)	439 (62.0)	**0.035**	**0.03**
Smoker	1007 (33.8)	507 (37.0)	269 (38)		
Kidney function					
eGFR (>= 60ml/min)	440 (18.3)	200 (18.6)	112 (19.4)	0.81	0.51
eGFR (< 60ml/min)	1970 (81.7)	875 (81.4)	464 (80.6)		
CCI					
0	1310 (43.9)	705 (51.5)	324 (45.8)		
1	805 (27)	358 (26.2)	169 (23.9)	**0.000**	0.24
>1	868 (29.1)	306 (22.4)	215 (30.4)		
Number of antihypertensive drugs					
1	2238 (75)	1054 (77)	520 (73.4)		
2	530 (17.8)	238 (17.4)	142 (20.1)	0.06	0.32
>2	215 (7.2)	77 (5.6)	46 (6.5)		

BMI, body mass index; eGFR, estimated glomerular filtration rate.
[a] Prevalent depression vs non-depressed patients
[b] New-onset depression vs non-depressed patients

Table 7-22 Baseline characteristic of eligible patients (N=3691)

Variable	M (SD)/ N (%)
Age at first prescription (years)	58.40 (13.4)
BMI	28.71 (5.7)
Cholesterol	5.71 (1.04)
Gender	
Male	1910 (51.7)
Female	1781 (48.3)
Smoking	
Non-smoker	2415 (65.4)
Smoker	1276 (34.6)
Kidney function	
eGFR (≥60ml/min)	552 (15)
eGFR (<60ml/min)	2434 (65.9)
Charlson comorbidity index score	
0	1634 (44.3)
1	974 (26.4)
>1	1083 (29.3)
Number of antihypertensive drugs	
1	2758 (74.7)
2	672 (18.2)
>2	261 (7.1)

BMI, body mass index; eGFR, estimated glomular filtration rate. Continuous data are presented in mean (M)/ slandered deviation (SD), Categorical data are presented in numbers (%).

Table 7-23 Baseline characteristic of the eligable patients (n= 3691) stratified by index antihypertesive drug regimen

Variable	α-blocker (N= 252)	DHP CCB (N= 741)	Non DHP CCB (N=78)	BB (N=442)	ACEI (N=1058)	ARB (N= 481)	MRA (N=139)	Diuretic (N=349)	Other (N=151)	*P*-Value
Age at first prescription (years)	64.29 (11.03)	59.39 (12.95)	63.59 (11.03)	56.96 (15.56)	54.84 (13.69)	58.72 (12.39)	63.61 (10.27)	60.91 (12.59)	58.87 (11.81)	**0.000**
Female sex	1111 (44)	373 (50.3)	179 (51.3)	238 (53.8)	484 (45.7)	226 (47)	67 (48.2)	179 (51.3)	60 (39.7)	**0.02**
BMI	29.02 (6.71)	28.54 (5.74)	28.91 (5.6)	28.21 (5.06)	28.24 (5.21)	28.21 (5.05)	30.63 (6.5)	28.72 (5.32)	29.44 (5.89)	**0.000**
Cholesterol	5.72 (1.15)	5.75 (1.10)	5.81 (1.12)	5.62 (0.93)	5.72 (1.00)	5.70 (1.06)	5.61 (1.18)	5.73 (1.05)	5.66 (1.09)	0.50
Smoking	105 (41.7)	271 (36.6)	28 (35.9)	151 (34.2)	325 (30.7)	158 (32.8)	64 (46)	115 (33)	59 (39.1)	**0.002**
eGFR (< 60 ml/min)	158 (74.5)	500 (82)	50 (76.9)	288 (81.4)	681 (85)	337 (83.2)	97 (77.6)	223 (78.2)	100 (77.5)	**0.011**
Charlson index score										
0	69 (27.4)	316 (42.6)	233 (29.5)	213 (48.2)	582 (55)	198 (41.2)	39 (28.1)	124 (35.5)	70 (46.4)	**0.000**
1	87 (34.5)	184 (24.8)	26 (33.3)	99 (22.4)	245 (23.2)	138 (28.7)	44 (31.7	105 (30.1)	46 (30.5)	
>1	96 (38.1)	241 (32.5)	29 (37.2)	130 (29.4)	231 (21.8)	145 (30.1)	56 (40.3)	120 (34.4)	35 (23.2)	
Number of antihypertensive drugs										
1	202 (80.2)	589 (79.5)	67 (85.9)	308 (69.7)	683 (64.6)	368 (76.5)	128 (92.1)	280 (80.2)	133 (88.1)	**0.000**
2	35 (13.9)	120 (16.2)	8 (10.3)	102 (23.1)	244 (23.1)	88 (18.3)	10 (7.2)	52 (14.9)	13 (8.6)	
>2	15 (6.0)	32 (4.3)	3 (3.8)	32 (7.2)	131 (12.4)	25 (5.2)	1 (0.7)	17 (4.9)	5 (3.3)	

α-blocker, Alpha-blocker; ACEI, Angiotensin converting enzyme inhibitor; ARB, Angiotensin II receptor blockers; BB, β-blockers; BMI, body mass index; CCB, calcium channel clocker; DHP, dihydropyridine; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoids. X^2 test and 1-way ANOVA test were used for categorical and continuous variables respectively

7.4.4.1 Association between antihypertensive drugs used as monotherapy or as part of polytherapy and risk of incident depression

The Cox proportional hazard method was used to calculate the risk of developing incident depression over the follow-up period based on the index antihypertensive drug. Figure 7-17 show the unadjusted Kaplan–Meier event-free survival curves. The log-rank test indicates that there were no statistically significant differences between antihypertensive drugs and depression rates (p = 0.081).

The results of the univariate and multivariate Cox proportional hazard models are displayed in Table 7-24. The univariate results showed that compared to the ACEI group, BB, dihydropyridine CCB and diuretics were associated with a statistically significant increased risk of incident depression, with the corresponding HRs of 1.45 (p = 0.013), 1.36 (p = 0.018) and 1.42 (p = 0.034). Although these trends were in the predicted direction in the multivariate model after adjusting the covariates in Model 2, the association with depression remained statistically significant only for the dihydropyridine CCB (HR = 1.38 95% CI 1.03–1.86, p = 0.03), while marginal associations between BB, diuretics and depression were observed (p = 0.07 and 0.049, respectively). As shown in the adjusted survival plot (Figure 7-18) the non-dihydropyridine CCB group shows the highest HR compared to ACEI, but this does not attain statistical significance and may be a reflection of the relatively small number of individuals among the non-dihydropyridine CCB group. Sensitivity analyses were performed where patients were censored at 3.5 years (Table 7-25). The results are very similar to those derived from the monotherapy analysis, showing that dihydropyridine CCB has a statistically significant relationship at 3.5 years. Overall, these results are in line with the findings obtained from the multivariate Cox proportional hazard model of the monotherapy analysis, demonstrating that CCB, is associated with a higher risk compared to ACEI.

The GEE analysis was used to account for the correlation between multiple antihypertensive drug classes prescribed subsequently to the index antihypertensive drug for each patient. The results of the GEE analysis showing the association between antihypertensive drug classes and the risk of depression are presented in Table 7-26. The findings are consistent with those of the Cox regression in the multivariate model, revealing that dihydropyridine CCB was associated with significantly greater odds of depression in the univariate model

(OR = 1.26, 95% CI 1.05–1.50, p = 0.02) and after controlling for other covariates in the multivariate model (OR = 1.32, 95% CI 1.06–1.64, p = 0.01). Diuretics also showed a statistically significant association in the univariate and multivariate models (OR = 1.45, 95% CI 1.12–1.87, p = 0.004). Regarding the other covariates, gender and smoking status at baseline were significant predictors for depression incidence in the multivariate model. The BMI showed a strong association in the univariate model, but after controlling for other covariates, the association lost significance (p = 0.06). Increasing number of antihypertensive drugs was not statistically significant (OR = 0.98, 95% CI 0.82–1.17, p = 0.85). The sequence of antihypertensive drugs was introduced in the model as a variable to explore whether prescription antihypertensive drugs subsequent to the index drug influence the association between the index antihypertensive drug and incidence of depression. As shown in Table 7-26 the sequence covariate has a statistically significant negative correlation with depression, which perhaps reflects that the risk of inducing depression is more likely related to the index antihypertensive drug or the duration of exposure to the antihypertensive drug.

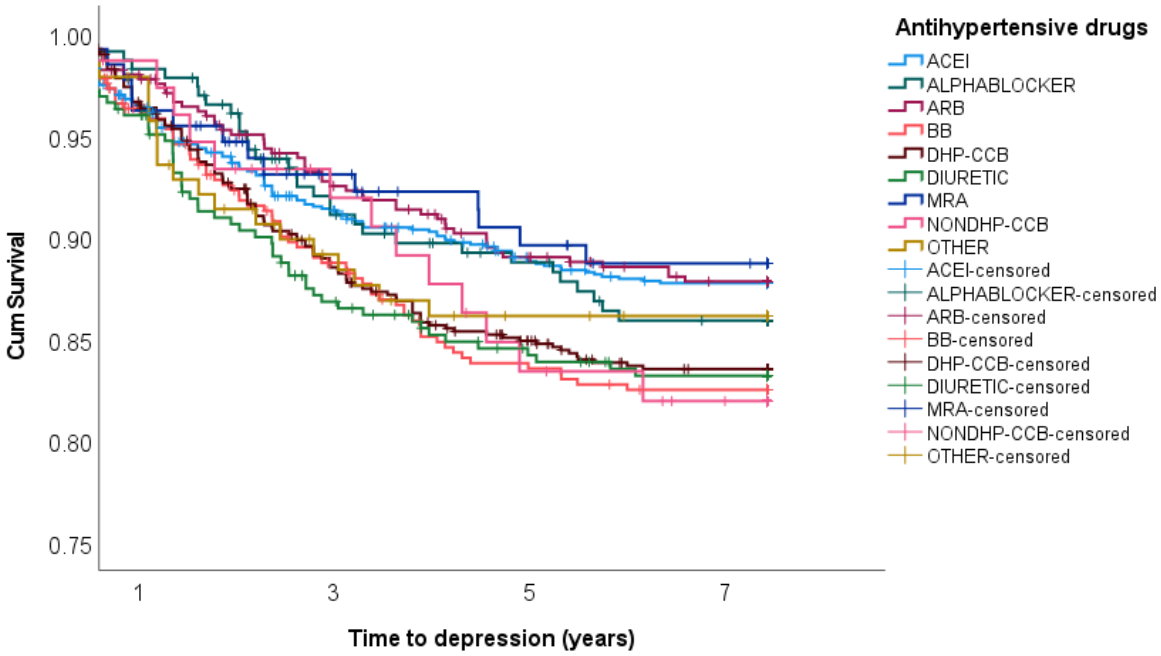

Figure 7-17 Unadjusted Kaplan Meier curves for onset of depression as indicated by receipt of antidepressants prescriptions, by first/index antihypertensive classes in hypertensive patients newly treated with antihypertensive medication.

Table 7-24 Cox PH model results for risk of depression and different antihypertensive medication classes among patients on antihypertensive poly therapy

			Univariate		Model 1		Model 2	
	Events/Total (%)	Incident rate per 1000 person-year	**HR (95%CI)**	***p*-value**	**HR (95%CI)**	***p*-value**	**HR (95%CI)**	***p*-value**
Antihypertensive class								
ACEI	173/1058 (16.3)	26.7	**Ref (1)**		**Ref (1)**		**Ref (1)**	
Alpha blocker	51/252 (20.2)	34.5	1.12 (0.75, 1.66)	0.57	1.21 (0.81, 1.81)	0.34	1.31 (0.85,2.01)	0.21
ARB	84/481 (17.4)	28.5	0.97 (0.71, 1.34)	0.88	1.01 (0.72, 1.39)	0.97	1.04 (0.73,1.49)	0.81
BB	99/442 (22.3)	38.9	1.45 (1.08, 1.97)	**0.013**	1.41 (1.05, 1.89)	**0.023**	1.36 (0.96,1.91)	0.075
DHP-CCB	161/741 (21.7)	36.7	1.36 (1.05, 1.76)	**0.018**	1.38 (1.06, 1.79)	**0.015**	1.38 (1.03,1.86)	**0.03**
Diuretics	76/349 (21.7)	38.2	1.42 (1.03, 1.96)	**0.034**	1.45 (1.05, 2.00)	**0.025**	1.44 (1.00,2.09)	**0.049**
MRA	20/139 (14.3)	24.7	0.91 (0.52, 1.57)	0.73	0.94 (0.54,1.65)	0.84	0.96 (0.54,1.71)	0.89
NONDHP CCB	15/78 (19.2)	32.3	1.45 (0.82, 2.57)	0.20	1.51 (0.84, 2.68)	0.16	1.67 (0.91,3.09)	0.09
Other antihypertensive drugs	29/151 (19.2)	33.2	1.16 (0.72, 1.88)	0.54	1.24 (0.76,2.01)	0.38	1.15 (0.67,1.96)	0.61
Total	708/3691 (19.2)	32.25						
Variables								
Age			0.99 (0.98,1.00)	0.07	0.99 (0.97, 0.99)	**0.03**	0.99 (0.98, 1.00)	**0.12**
Female			1.58 (1.32,1.90)	0.00	1.58 (1.32, 1.90)	0.000	1.62 (1.32, 1.99)	**0.00**
BMI			1.02 (1.002,1.03)	0.03	1.02 (1.002,1.03)	**0.03**	1.01 (0.99,1.03)	0.08
Smoking			1.25 (1.04, 1.50)	0.02	1.25 (1.04,1.50)	**0.01**	1.41 (1.15, 1.72)	**0.001**
eGFR			0.87 (0.68,1.12)	0.28	0.87 (0.68,1.12)	0.28	0.88 (0.68,1.14)	0.35
Cholesterol			0.97 (0.89, 1.06)	0.55	0.97 (0.89,1.06)	0.55	0.97 (0.81, 1.16)	0.52
CCI			0.94 (0.85,1.05)	0.32	0.94 (0.85,1.05)	0.32	0.98 (0.83, 1.18)	0.91
Number of antihypertensive drugs			0.98 (0.85,1.14)	0.84	0.98 (0.84,1.14)	0.84	0.97 (0.81,1.16)	0.76

Model 1 adjusted for age and gender. Model 2 adjusted for age, gender, BMI, smoking, eGFR, cholesterol and Charlson comorbidity index. Abbreviations: ACEI, Angiotensin converting enzyme inhibitor; ARB, Angiotensin II receptor blockers; BB, β-blockers; BMI, body mass index; CCB, calcium channel clocker; CCI, Charlson comorbidity index; CI, confidence interval; DHP, dihydropyridine; eGFR; estimated glomerular filtration rate; HR, hazard ratio; MRA, mineralocorticoids.

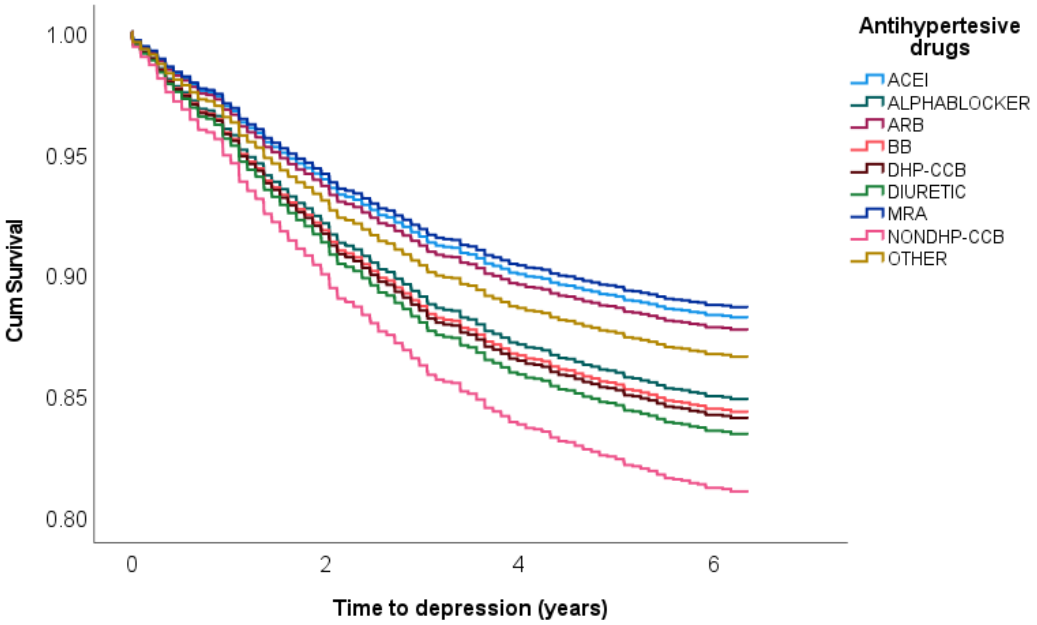

Figure 7-18 Adjusted survival plot for onset of depression as indicated by receipt of antidepressants prescriptions, by index antihypertensive drug classes in newly treated hypertensive patients.

Table 7-25 Sensitivity analysis patients right censored at 3.5 years censoring point

	Events/Total (%)	Incident rate per 1000 person-year	Univariate		Model 1		Model 2	
			HR (95%CI)	***p*-value**	**HR (95%CI)**	***p*-value**	**HR (95%CI)**	***p*-value**
Antihypertensive class								
ACEI	91/1058 (8.6)	**31.3**	**Ref (1)**		**Ref (1)**		**Ref (1)**	
Alpha blocker	21/252 (8.3)	30.5	0.98 (0.61, 1.58)	0.95	1.07 (0.66, 1.73)	0.78	1.13 (0.67,1.89)	0.65
ARB	34/481 (7.1)	25.4	0.82 (0.55, 1.22)	0.33	0.85 (0.57, 1.26)	0.42	0.85 (0.55, 1.33)	0.49
BB	48/442 (10.9)	40.7	1.31 (0.93, 1.86)	0.12	1.27 (0.89, 1.81)	0.17	1.19 (0.79, 1.79)	0.38
DHP-CCB	84/741 (11.3)	41.6	1.34 (1.00, 1.81)	**0.049**	1.36 (1.01, 1.84)	**0.04**	1.43 (1.03,2.01)	**0.03**
Diuretics	43/349 (12.3)	46.7	1.49 (1.04, 2.15)	**0.03**	1.53 (1.06, 2.21)	**0.02**	1.61 (1.07, 2.42)	**0.02**
MRA	10/139 (7.2)	26.3	0.83 (0.43, 1.61)	0.59	0.87 (0.45, 1.69)	**0.68**	0.91 (0.46, 1.78)	0.77
NONDHP CCB	6/78 (7.7)	27.7	0.86 (0.38, 1.97)	0.73	0.90 (0.39, 2.07)	0.81	0.92 (0.36, 2.28)	0.85
Other antihypertensive drugs	17/151 (11.3)	42	1.35 (0.81, 2.27)	0.25	1.44 (0.86, 2.43)	0.16	1.29 (0.72,2.32)	0.38

Model 1 adjusted for age and gender. Model 2 adjusted for age, gender, BMI, smoking, eGFR, cholesterol and Charlson comorbidity index. Abbreviations: ACEI, Angiotensin converting enzyme inhibitor; ARB, Angiotensin II receptor blockers; BB, β-blockers; BMI, body mass index; CCB, calcium channel clocker; CI, confidence interval; DHP, dihydropyridine; eGFR; estimated glomerular filtration rate; HR, hazard ratio; MRA, mineralocorticoids;

Table 7-26 Results of generalised estimating equation (GEE) models showing the association between antihypertensive drug classes and odds of having new-onset depression among patients on antihypertensive polytherapy

	Unadjusted		Model 1		Model 2	
	OR (95%CI)	**p-value**	**OR (95%CI)**	***p*-value**	**OR (95%CI)**	***p*-value**
Antihypertensive class						
ACEI	**Ref (1)**		**Ref (1)**		**Ref (1)**	
Alpha blocker	1.31 (0.99,1.71)	0.05	1.34 (1.02, 1.77)	0.03	1.43 (1.04, 1.95)	0.03
ARB	1.08 (0.87,1.35)	0.43	1.09 (0.88, 1.35)	0.42	1.17 (0.91, 1.51)	0.22
BB	1.22 (0.98,1.52)	0.07	1.21 (0.97, 1.51)	0.09	1.15 (0.88, 1.50)	0.28
DHP CCB	1.26 (1.05,1.50)	**0.02**	1.27 (1.06,1.52)	**0.01**	1.32 (1.06, 1.64)	**0.01**
Diuretics	1.26 (1.03,1.55)	**0.03**	1.28 (1.04, 1.58)	**0.02**	1.45 (1.12, 1.87)	**0.004**
MRA	0.87 (0.59,1.29)	0.49	0.92 (0.62, 1.37)	0.69	0.95 (0.61, 1.47)	0.82
NONDHP CCB	1.41 (0.92,2.15)	0.18	1.42 (0.92, 2.18)	0.12	1.46 (0.88, 2.41)	0.13
Other antihypertensive drugs	1.18 (0.82,1.71)	0.36	1.27 (0.88, 1.83)	**0.00**	1.02 (0.66, 1.56)	0.93
Variables						
Age	0.998 (0.991,1.00)	0.47	0.99 (0.98, 1.00)	0.21	0.99 (0.98, 1.004)	0.17
Female	1.74 (1.43,2.10)	**0.00**	1.75 (1.45, 2.12)	**0.000**	1.88 (1.53, 2.33)	**0.00**
BMI	1.02 (1.003,1.04)	**0.02**	1.02 (1.00, 1.04)	**0.02**	1.02 (0.99, 1.04)	0.06
Smoking	1.19 (0.98,1.44)	0.07	1.28 (1.05, 1.55)	**0.014**	1.38 (1.12, 1.71)	**0.002**
eGFR	0.93 (0.72,1.21)	0.61	0.95 (0.73, 1.25)	0.75	0.99 (0.72, 1.26)	0.74
Cholesterol	1.03 (0.94, 1.13)	0.51	1.03 (0.94, 1.13)	0.51	1.01 (0.92, 1.11)	0.79
CCI	1.005 (0.89,1.13)	0.93	1.05 (0.88, 1.24)	0.58	1.00 (0.83, 1.21)	0.97
Number of antihypertensive drugs	0.97 (0.84,1.12)	0.74	0.96 (0.83, 1.10)	0.54	0.98 (0.82, 1.17)	0.85
Sequence of the antihypertensive drug	0.90 (0.80, 1.01)	0.07	0.88 (0.78,0.99)	0.04	0.87 (0.78, 0.97)	**0.012**

α-blocker, Alpha-blocker; ACEI, Angiotensin converting enzyme inhibitor; ARB, Angiotensin II receptor blockers; BB, β-blockers; BMI, body mass index; CCB, calcium channel clocker; CCI, Charlson comorbidity index; CI; confidence interval; DHP, dihydropyridine; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoids; OR, odd ratio

7.5 Discussion

The purpose of the current study was to investigate the relationship between antihypertensive drug classes and the risk of incident depression in a middle-aged hypertensive population attending to a secondary care hypertension clinic over a 7-year period. This question was addressed in several ways. First, I examined the association between the five major classes of antihypertensive drugs as monotherapy and the risk of incident depression. If a causal relationship between an individual class and depression indeed exists, a dose-response relationship may be expected. Second, I therefore also investigated whether higher doses of antihypertensive drugs were associated with a higher risk of developing depression. Finally, to ensure consistency in the results and delineate the type of association between antihypertensive drug subclasses and depression, an additional analysis of antihypertensive polytherapy was conducted. In this analysis, the effect of individual major classes and subclasses of antihypertensive drugs, used as either monotherapies or as a part of antihypertensive polytherapies, on depression was investigated after adjusting for the baseline polytherapy of antihypertensive drugs and their prescription sequencing.

7.5.1 Antihypertensive monotherapy and risk of depression incidence

In this cohort of 2406 newly treated hypertensive patients with no previous history of antihypertensive or antidepressant prescriptions followed for 7 years by the GBPC, my findings demonstrated that compared to the ACEI group, CCB monotherapy was significantly associated with increased risk of depression incidence (HR = 1.38; 95% CI 1.07–1.80; p = 0.014), which is consistent with my hypothesis. This association remained stable after conducting additional analysis excluding events that occurred within the first year of follow-up (HR = 1.38; 95% CI 1.03–1.85; p = 0.03), excluding patients with a prevalent CVD and those who developed CVD during the exposure period (HR = 1.45; 95% CI 1.06–1.95; p = 0.017) and after restricting the analysis to patients who received six or more antidepressant prescriptions within the first 12 months from the index date (HR = 1.6;3; 95% CI 1.01–2.63; p = 0.047). This finding is consistent with prior studies suggesting that CCB may be associated with an increased risk of mood disorders (Boal et al., 2016) and for developing depression and/or initiating

antidepressant treatment (Cao et al., 2019, Shaw et al., 2019). Nevertheless, it contrasts some other published studies. A cross-sectional study of 14,195 elderly patients with no previous history of CVD or HF found no association between CCB and depressive symptoms as measured by the CES-D scale (Agustini et al., 2020). Moreover, a cohort study conducted by Tully et al. (2018) suggested that CCB may be effective as adjunctive therapy for the treatment of depression and cognitive dysfunction. In line with these findings, (Kessing et al., 2020) showed that CCB as a general class is associated with a reduced incident rate of depression. The researchers further reported that among this drug class, amlodipine and verapamil in particular were associated with a lower rate of incident depression. Controversies also remains within findings derived from pre-clinical research (Nanou and Catterall, 2018, Clark et al., 2020, Korczak et al., 2020, Normann et al., 2018, Giansante et al., 2020). After the discovery of the risk gene within the L-VGCC variation (i.e. CACNA1C) as being involved in psychiatric diseased, calcium channel seems a promising target in modulating depressive disorders, though the exact role of L-VGCC blockades, hence their clinical effect in the context of depression remains to be elucidated. It is well known that L-VGCC is involved in several neurobiological functions which are differed based on the L-VGCC subtypes, isoforms and their brain localisation. Recently Clark et al. (2020) proposed that the CACNA1C in human brain is highly complex after identifying 38 novel exons and 241 novel transcripts within this gene. Accordingly, we would expect that blockade of L-VGCC would not produce a unifying pharmacological effect on the brain level. Findings from the current study suggests a higher risk of depression incident within CCB therapy compared to ACEI therapy, However, until further investigations perhaps it will be unwise to draw a firm conclusion regarding the relationship between the currently available CCB and depression.

Contrary to my hypothesis, the results from this study showed that BB was not associated with incident depression in comparison with the ACEI group (HR = 1.17; 95% CI 0.86–1.59; $p = 0.31$). My findings are consistent with previous studies suggesting that BB in general has no effect on depression or that the effect might be trivial (Battes et al., 2012, Bright and Everitt, 1992, Carney et al., 1987, Ko et al., 2002, Luijendijk et al., 2011, Verbeek et al., 2011). By contrast, my results also contradict the conclusions of several recent studies providing evidence that points towards the involvement of BB in mood disorders, including depression

(Agustini et al., 2020, Boal et al., 2016, Cao et al., 2019, Shaw et al., 2019). Other studies have suggested that antidepressant activity is a specific feature to lipophilic BBs, such as propranolol (Johnell and Fastbom, 2008, Ringoir et al., 2014, Shaw et al., 2019). Nevertheless, in a very large case-control study, Kessing et al. (2020) refuted the BB-induced depression theory and suggested that BB as a drug class is associated with a decreased risk of incident depression and that propranolol, carvedilol, bisoprolol and atenolol are the drugs within this class with the lowest statistically significant risk of incident depression (Kessing et al., 2020). Notably, these drugs have varying lipid solubility; therefore, according to the authors, they may induce an antidepressogenic effect that is independent of their lipid solubility (Kessing et al., 2020). As previously noted, depression is correlated with poor cardiac prognosis and a high mortality rate, particularly in CVD patients. Thus, medications that are associated with an increased risk of depression might be an important consideration for physicians treating these patients. Indeed, Kim et al. (2019a) showed that even though BBs are recommended for patients with HF, the use of these medications was lower among those with co-morbid depression, resulting in a reduced survival rate in these patients. Although my findings do not support that BBs are associated with incident depression, confounding due to health improvement cannot be ruled out. On the other hand, my results may indicate that any benefit of BBs might outweigh the negative impact on mood. Since quality of life may be considered just as important as length of life, future studies could examine the extent to which BBs affect mental health and quality of life in CVD patients.

Furthermore, the current study provides no evidence that TZD can induce depression (HR = 1.04; 95% CI 0.77–1.43; p = 0.77), in line with previous work (Boal et al., 2016, Johnell and Fastbom, 2008, Kessing et al., 2020, Shaw et al., 2019). Likewise, the ARB group showed no statistically significant differences in depression risk compared to the ACEI group (HR = 1.17; 95% CI 0.86–1.59; p = 0.31). Because my study design lacks an untreated control group, it is difficult to compare my results with those of previous studies in the literature. My findings do not provide clear evidence of whether ACEI/ARB have any favourable effect against depression; however, the dose-response analysis in the present study suggested that ACEI and ARB may each have a distinct effect on depression (Section 7.5.3). In the literature, observational studies have examined ACEI and

ARB as a combined group relative to a control group and have provided evidence that these antihypertensive classes may be associated with decreased incidence of depression (Kessing et al., 2019), decreased rates of antidepressant use (Nasr et al., 2011) and decreased risk of hospital admission due to mood disorders (Boal et al., 2016). In contrast, findings from a large and more recent prospective study of 1.8 million patients showed that RAS blockade was associated with increased risk of depression, although this association was relatively weak (Shaw et al., 2019). Another study has reported a null association between RAS blockade and the use of antidepressants; however, the authors observed a significantly lower risk of antidepressant use among specific groups of patients, particularly those with diabetic nephropathy (Ahola et al., 2014). Kessing et al. (2020) showed that ACEI and ARB are generally associated with reduced risk of depression and out of these two classes, only enalapril and ramipril have shown a significant risk reduction of incident depression.

7.5.2 Antihypertensive polytherapy and risk of depression incidence

This study aimed to expand my previous analysis to provide a better sense of the whole picture. This was a prospective cohort study enrolling 3691 treated hypertensive patients attending the GBPC and were followed up for 7 years. In this additional analysis CCB class were further stratified into dihydropyridine and non-dihydropyridine. Two types of analysis were performed including the GEE and survival analysis. Overall, findings from the current study do not support early evidence suggesting that dihydropyridine possess antidepressants effect (Casamassima et al., 2010). By contrast it showed that in comparison to ACEI, dihydropyridine subclass of CCB as a mono or part of antihypertensive poly therapy increase the risk of incident depression (HR= 1.38, 95%CI 1.03, 1.86 *p*-value=0.03), which is consistent with the results of the monotherapy analysis. The GEE analysis further reaffirms and bolsters my findings demonstrating that dihydropyridine CCB is associated with a significant increased risk of depression while controlling for demographic variables, baseline number of antihypertensive drugs and their sequencing (OR= 1.32 95%I 1.06, 1.64 *p*-value=.0.01).

In the literature, studies investigating the effect of dihydropyridine, non-dihydropyridine each separately in relation to depression has been scarce, making

the comparison of my findings to other a bit of challenging. However, the result is in line with recent evidence generated from preclinical studies proposing that dihydropyridine CCB is implicated in depression pathogenesis (Nanou and Catterall, 2018, Qian et al., 2017, Zhou et al., 2017). On balance, not all member of this subclass may have the same effect in human. In a pair of a double blind placebo RCT, Taragano et al., found that nimodipine was superior to placebo in reducing depression symptoms and lowering the rates of depression recurrence (Taragano et al., 2001, Taragano et al., 2005). Kessing et al., also showed that amlodipine may reduce the risk of new-onset depression. Altogether, these evidences present how data generated from animal and humans are varied complicating their interpretation and clinical implication.

Unexpectedly, diuretics also showed a trend toward increased risk of depression in both survival and GEE analysis. As mentioned previously, most evidence reported a null association between diuretics and depression, though very few reported positive correlations(Cao et al., 2019, Okada, 1985). One explanation for this odd results is perhaps due to the underlying missing data. About 20% of the patient's data related to eGFR variable was missing in this cohort. In the diuretic group, eGFR missing data represents 22%, whereas 80% of those patients did not develop depression. Thus, excluding those patients from the model would lead to overestimation of the diuretic effect. I re-run the GEE analysis and omit the eGFR variable. Result showed non statistically significant association with depression but a trend association between dihydropyridine and depression was observed (*p*-value= 0.055, data not shown).

7.5.3 **Dose-response realtionship**

The results of my dose-response relationship need to be considered in relation to the inherent limitations in the calculation of DDD from the available data. The prescription data available included only data on dispensed drugs – number dispensed and the tablet strength. There were no data on the prescribed dose. Hence one of the assumptions in calculating DDD was based on the defined average dose for each drug. Whilst this is not accurate and may over- or underestimate drug exposure, it gives a crude estimate of drug exposure. Another major limitation of the dose-response analysis is that there is no indicator of actual drug adherence. Whilst prescription encashment indicates that the patient has

received the drug, this does not imply that the patient has actually taken the drug as prescribed. Because my results from the primary analysis suggested that CCB is associated with a higher risk of depression, I expected a similar link pattern in the dose-response analysis. Contrary to my expectation, a higher level of cDDD of CCB did not show an association with an increased risk of depression. Similarly, BB dose-response analysis showed that depression incidence tended to be lower among patients in the higher tertile of the cDDD compared to the lower tertile in the subgroup analysis of BB users, although this did not attain statistical significance (HR = 0.6; 95% CI 0.34–1.04; p = 0.07). Participants in the lower tertile were predominantly female, representing around 80% of the patients; however, the association persisted after adjusting for this confounder in the multivariate model. In line with this result, Battes et al. (2012) examined the association between BB therapy and depressive symptoms in PCI patients. They demonstrated that after 12 months, the patients treated with BB were less likely to experience depressive symptoms compared to the control group and that there was a dose-response relationship between BB and depressive symptoms, with a higher dose providing a more pronounced protective effect. Altogether, these observations—including my findings—are consistent with those reported by Kessing et al. (2020).

One of the most important conclusions of this chapter is that ACEI and ARB may not have the same effect on depression. The results of the dose–response analysis showed that the patients who received higher cDDD of ARB were at increased risk of subsequent depression compared to those who received low cDDD of ARB. This might indicate that depression is related only to high levels of the therapeutic dose of ARB. Although this finding slightly differs from those of Kessing et al., showing that none of the individual drugs within the ARB group is associated with depression risk, it can be argued that Kessing et al. measured the risk of depression in relation to the number of prescriptions. While the cDDD may simply reflect a patient's compliance with their increasing number of prescriptions, they are two different measures of drug exposure. Additionally, my result was derived after having adjusted for the number of prescriptions during the exposure period. Both ACEI and ARB belong to the same class and have been shown to be equivalent in their blood pressure lowering effect (Yusuf et al., 2008). Thus, it is reasonable to study them as a combined group, but does this apply when assessing depression

as an outcome? The following section suggests a different perspective, based on findings from studies that evaluated the effect of ACEI and ARB separately on mental health outcomes. A previous nested case-control study showed an increased risk of suicide among ARB users but not ACEI users, although this study was limited by the very small number of patients receiving ARB and was not intended to investigate a priori the link between ACEI, ARB and suicide (Callréus et al., 2007). Nonetheless, this finding was supported by Mamdani et al. (2019), who conducted a nested case-control study matching 964 cases to 3856 controls aged 66 years and older, who were exposed to either an ACEI or ARB. They found that patients receiving ARB were at a greater risk of suicide (OR = 1.63; 95% CI 1.33–2.00) than those receiving ACEI. Nonetheless, the notion that ARB may elevate suicide risk has been challenged recently, and evidence suggests that there are no significant differences between ACEI and AEB in this regard (Dent et al., 2020, Lin et al., 2020). Agustini and colleagues investigated the association of different antihypertensive drugs and their combinations with the presence of depressive symptoms in a cross-sectional study enrolling 14,195 older individuals (Agustini et al., 2020). They found that out of all possible combinations, only the combination of ARB and BB was significantly associated with depressive symptoms (OR = 1.62; 95% CI 1.18–2.22; $p < 0.01$) compared to non-medicated patients or those on diuretics. Other studies have suggested that among the RAS agents, ACEI may be the group most likely to be involved in the pathology of depression. A retrospective cohort enrolling 181,709 patients who were newly diagnosed with hypertension examined the associations of different classes of antihypertensives with the risk of depression over a median of 4.3 years of follow-up. In contrast to my results, they found that the incidence of depression among ACEI users was higher than among ARB users. Nasr et al. (2011) also observed that patients treated with ARB were at lower risk for subsequent antidepressant use compared to patients treated with ACEI.

One explanation for these inconsistent findings might be that ACEI and/or ARB can act through a biological pathway that is independent of RAS. A preclinical study by Luo et al. (2020) demonstrated that unlike ARB and renin inhibitors, ACEI may function as an antidepressant via a non-RAS mechanism. The authors used chronic unpredictable stress and chronic social defeat stress to induce depressive-like behaviour in rodents. They found that ACEI initiated antidepressant activity by

activating bradykinin, a degraded substrate of ACE, which in turn activated the bradykinin 2 receptor and subsequently stimulated cell division cycle 42. The later is a protein kinase that regulates the activation of the mTORC1 signalling pathway, which is critical in the synaptic mechanisms underlying rapid-acting antidepressants. Consequently, this study concluded that ACEI may emerge as a novel fast-onset antidepressant.

As aforementioned, most previous studies evaluated that the effects of ACEI and ARB as antihypertensive drugs belonged to the same class; their effects have rarely been considered separately. Therefore, it is important to keep in mind that, while my results indicating that the effect of ACEI and ARB may not be equivalent in the context of depression and that each could exert distinct effects on mental health agree with some of the literature, they should be interpreted as preliminary until future investigations are able to replicate the findings—with respect to the dose in particular, as the trend is only marginally significant.

It should be noted that all the clinical studies described above, including my study, evaluated RAS agents as a potential preventive intervention for depression. The literature on the antidepressant activity of RAS agents in populations with depression is limited and reports inconsistent findings (Brownstein et al., 2017, Fujiwara et al., 2017, Köhler-Forsberg et al., 2020, Pavlatou et al., 2008). In a recent matched prospective cohort study, Köhler-Forsberg et al. (2020) investigated whether a combined treatment of RAS agents and SSRIs was associated with a reduced risk of psychiatric hospital contacts compared to the use of SSRIs alone. The main finding from this study showed that patients treated with RAS agents plus SSRIs were at lower risk for any psychiatric hospital contacts (HR = 0.91; 95% CI 0.84–0.98) compared to patients treated with SSRIs alone, and there was no apparent difference in the risk of suicide (HR = 1.06; 95% CI 0.79–1.42) or risk of hospital contact due to depression (HR = 0.92; 95% CI 0.80–1.05). This study examined the combined effect of ACEI and ARB; thus, a clear picture of how each group might act on depression cannot be determined. Furthermore, the main outcome in most of the previously mentioned observational studies examining the effect of ACEI/ARBs was MDD (Boal et al., 2016, Cao et al., 2019, Kessing et al., 2019, Kessing et al., 2020, Köhler-Forsberg et al., 2020, Shaw et al., 2019). Regarding depressive symptoms, a meta-analysis of six RCTs showed that RAS blockade was associated with improved quality of life in terms of mental

health; however, there were no differences in terms of depressive symptoms (Brownstein et al., 2017). Some other studies have found that certain RAS agents were associated with improving depressive symptom scores (Fujiwara et al., 2017, Pavlatou et al., 2008). This improvement would have been undetectable in studies measuring depression as a clinical diagnosis and/or antidepressant initiation, which gives rise to the question of whether some RAS agents are effective as therapeutic and/or as preventive interventions for mild (but not for severe) cases of depression.

It is important to note that while several studies have investigated the association between antihypertensive drug classes and depression, only a few have considered evaluating the dose response of antihypertensive drugs in relation to the occurrence of depression. Most comparable to the current investigation is the study conducted by Kessing et al. (2020). Because my work lacks an untreated comparison group, individuals with lower cDDD were set as the reference group, an approach similar, to some extent, to the one adopted by Kessing et al. (2020) where they set individuals with one or two prescriptions as the reference group. Nevertheless, this methodological approach is likely to be confounded by patient adherence. Table 7-27 presents the baseline characteristics of patients stratified according to the number of prescriptions received during the exposure period of the monotherapy analysis. As shown, the main variables that significantly varied across the three groups were age, SBP and CCI score. Patients with seven or more filled prescriptions were relatively older, predominantly stage 2-hypertensive patients and had higher CCI compared to the other two groups. I compiled the same table with the subgroups of the antihypertensive drug class, and the results were almost the same (data not shown). While the number of prescriptions does mirror the severity of elevated BP at baseline in my cohort, it may also be an indication of adherence during the exposure period. Perhaps the individuals diagnosed and labelled as stage-2 hypertensive were more committed to adhering to their medication than those with lower BP. Therefore, the reference group in Kessing et al. (2020), as well as the one in my study, may be confounded by adherence to medication.

Table 7-27 Baseline characteristics of 2406 patients based on number of prescriptions at baseline

	Number of prescriptions			
Variable	**1-3**	**4-6**	**≥7**	***p*-value**
Age (years)	51 (14.2)	50.36 (13.9)	52.29 (13.6)	**0.036**
Female sex	504 (41.1)	425 (34.7)	296 (24.2)	0.2
SBP,mmHg	156.37 (23.59)	156.84 (24.1)	160.1 (25.9)	**0.01**
DBP,mmHg	109.41 (32.2)	112 (34.5)	110 (33)	0.23
BMI	28.62 (5.6)	28.24 (5.3)	28 (50)	0.32
Cholesterol	5.7 (1.08)	5.7 (1.1)	5.8 (1.1)	0.08
Smoking	336 (39.4))	299 (35.1)	218 (25.6)	0.67
eGFR (< 60ml/min)	672 (40.8)	611 (37.1)	364 (22.1)	**0.00**
Charlson index score				
0	417 (44)	395 (45.6)	222 (37.5)	
1	246 (25.9)	216 (24.9)	171 (28.9)	**0.038**
>1	285 (30.1)	255 (29.4)	199 (33.6)	

BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure. X^2 test and 1-way ANOVA test were used for categorical and continuous data respectively.

7.5.4 **Comparison with other studies**

Tremendous work has been done on this topic to elucidate the nature of the association between different classes of antihypertensive drugs and depression. I summarised the main studies in the literature focusing on one or multiple classes of antihypertensive drugs in the introductory chapter of this thesis, dedicating a section to each main drug class. I also compared my results with the main findings from these studies in the previous sections. Thus, in this sub-chapter, I shall only describe and discuss the studies that are similar to mine in terms of main objectives, outcomes and overall design. Altogether, two such cohorts published in recent years were found. Shaw et al. (2019) conducted a prospective cohort study enrolling 538,730 participants where new users of antihypertensive monotherapy were matched with an untreated comparator based on age, sex and area deprivation using a 1:1 ratio. Their study design was analogous to my monotherapy analysis. Eligible patients were free of antihypertensive prescriptions for six months, after which the antihypertensive treatment period started and lasted for up to 12 months, which is equivalent to the exposure period in my cohort. During this treatment window, the patients were on at least four prescriptions of antihypertensive drug monotherapy (each lasted for three months, so the four prescriptions covered a one-year period in total). This included any of the four major antihypertensive classes: CCB, BB, angiotensin antagonist and TZD. The patients on polytherapy were also eligible if during the

last 3 months of the treatment window, they received antihypertensive medication from two or more of the aforementioned antihypertensive drug classes. Patients with a prescription of psychiatric treatment during the antihypertensive treatment window or within the preceding 10 years were excluded from the cohort. The main outcome was treatment for new-onset depressive episodes, as indicated by the first prescription of antidepressants or hospital admission. The authors calculated the risk for incident depression based on five different time periods. Two of the most noticeable differences between the cohort design of Shaw et al. (2019) and mine is that my cohort lacked a control untreated group and the cumulative number of prescriptions during the exposure period in my study varied considerably between participants, with less than 25% having filled their prescriptions for more than 6 months and only 1.6% for the whole 12 months. On the other hand, as I mentioned above, Shaw et al. (2019) ensured that eligible participants received a consistent number of prescriptions covering all the antihypertensive treatment window (12 months), although this approach does not necessarily ensure better adherence. These methodological heterogeneities might create some discrepancies between my findings and those of Shaw et al. (2019) in several aspects. First, Shaw et al. (2019) showed that all monotherapy drugs were associated with a small elevated risk of incident depression—especially at the initial time of follow-up—a risk which declined over time, while I found that the risk of incident depression might be low during the initial period, in particular at the first two-year censoring point (data not shown), and might increase over time. However, this observation is likely due to the low number of events in my cohort during the first period, which translates to insufficient power to detect any statistical difference. Perhaps the low number of prescriptions in my cohort during the exposure period may indicate poor adherence, and consequently, the effect of antihypertensive drugs on depression was diluted. Nonetheless, the dose-response analysis showed no statistically significant differences in the depression incident rate for patients who had a higher level of cDDD compared to those who had a lower cDDD, suggesting that my findings are robust against this methodological approach. Second, the highest risk of incident depression in the study of Shaw et al. (2019) was observed among BB users at all time periods. This is perhaps unsurprising, knowing that the cardiovascular conditions of patients receiving BB as an initial drug are likely to be more complicated placing them at greater risk of depression than those of

patients newly started on CCB or RAS antagonist, the first-line therapy of hypertension. In the polytherapy analysis of my cohort, this problem was addressed by creating a sequence variable. The results showed that BB was associated with an elevated risk of depression; however, that was in comparison to ACEI, and it was only marginally significant. Finally, I also showed that antihypertensive polytherapy is not associated with an increased risk of developing depression, which also contradicts the findings of Shaw et al. (2019).

The second investigation similar to mine consisted of a nested-case control population-based study conducted more recently by Kessing et al. (2020). The authors enrolled 5.4 million participants to investigate the association between 41 individual antihypertensive drugs belonging to the five major classes (ACEI, ARB, CCB, BB and diuretics) and new-onset depression, defined as either a clinical diagnosis or the use of antidepressant drugs. This is the first study of its kind and of this size on this research subject. Kessing et al. (2020) adopted a methodological approach to minimise confounding by indication: they estimated the rate of depression during successive prescription periods of the drug, where the patients who had received a cumulative of three or more prescriptions of an antihypertensive drug were compared to a reference group, which included people who had only one or two prescriptions for the same drug. This method highlighted the bias related to confounding by indication, as patients who had one or two prescriptions showed increased HR of depression relative to individuals with a non-use period. Although this approach lowers this kind of bias to some extent, it can also increase other sources of bias, particularly those related to adherence (see Section 7.5.3). The main findings of this study revealed that neither the 5 major classes nor the individual 41 antihypertensive drugs within these classes were associated with an increased risk of depression incidents. Kessing et al. (2020) further indicated that nine of these medications were associated with a reduced risk of developing depression, which were therefore suggested to be considered in patients at high risk of depression. It is important to note that Kessing et al. (2020) had only compared the risk of depression across different prescription periods within each individual drug. Overall, my findings generated from the dose-response analysis agree with these results. Nevertheless, antihypertensive treatment persistence and/or duration may be an important factor in achieving long-term benefits, which may explain the overall depression

risk reduction in this study. Furthermore, given that the nine antihypertensive drugs recommended by Kessing et al. (2020) are from three different classes, it is possible that their global effect on depression was achieved through their common pharmacological effect on overall cardiovascular health rather than through an independent biological mechanism. The latter suggestion complements several other observations that have shown that the BP lowering effect is important in improving and/or reducing the risk of some neurological disorders, such as Alzheimer's disease (Ding et al., 2020), dementia (Hughes et al., 2020) and cognitive dysfunction (Forte et al., 2019), signifying the importance of BP in modulating these disorders, although the role of BP in depression pathogenesis has been less consistent. Another possible source of discrepancy is the variation in the targeted population. In the Kissing et al. (2020) study, the median age the particpants was >60 years; however, the participants' median age varied considerably across individual drugs. For example, the median age of the patients treated with propranolol, a candidate drug in this study, was 20 years. Those patients were very likely to be healthy individuals at baseline, with low severity or low chronicity of the treated illness. On top of that, even the type of illness being treated—and subsequently, the dosage regimen of propranolol—may differ from those in elderly patients on other antihypertensive drugs. By contrast, it should be stressed that the population in my study were participants attending hypertension clinic providing secondary and tertiary care service. From the clinical presentation of the participants data it can be anticipated that those patients are already at high risk of developing depression. They have complicated hypertension, multiple comorbidities, and family history of premature CVD which by it is self can trigger psychological stress (which is often associated with depressive symptoms). Altogether these complicated health condition can at least partly explain the higher incidence rate of depression in my cohort. Nevertheless, despite the potential source of bias in the current sample, given that several studies with different designs continued to publish contrasting results , this may raise the possibility that the relationship between antihypertensive drugs and depression may not be uniform across patients exposed to these drugs. One possible explanation is that the depression in CVD patients or those at high risk of CVD may represent a subtype of depression distinct from that in healthy individuals. CVD or high-risk CVD patients usually experience changes in normal cardiovascular function, whereby depression may stem from these pathological

roots. Accordingly, ameliorating and treating depressive symptoms in CVD and CVD high-risk populations may, in the first place, rely on controlling and effectively treating CVD and its potential risk factors. However, due to population heterogeneity across studies, it is unclear whether the reduced risk of depression noticed among patients receiving certain antihypertensive drug classes are due to an improvement in overall CVD health (such as BP, cardiac output, vascular resistance, cerebral perfusion, improvement of microvascular integrity and suppression of vascular atherosclerosis) or indeed due to a specific antidepressogenic activity related to the general class or to a particular medication within the drug class. Further investigation is required to elucidate the pharmacological role of different antihypertensive drugs in relation to depression in CVD- and CVD-free populations and whether cardiac conditions could evoke a distinct subtype of depression. Another reason may explain results discrepancies could be related to shared pathological origin between hypertension and depression that could facilitate or enhance the treatment of both conditions simultaneously. For example, extensive evidence has suggested that neuroimmune mechanisms, such as the hyperactivation of brain RAS and microglial neuronal cells, have a role in initiating and maintaining arterial hypertension (Calvillo et al., 2019, Hirooka, 2020, Llorens-Cortes and Touyz, 2020). In this case, agents acting on the RAS system may have a potential benefit over other antihypertensive drugs in managing hypertension. On the other hand, these neurobiological disruptions have been suggested to be linked to the pathogenesis of depression.Therefore, at least theoretically, it would be expected that patients with hypertension that involves the disruption of these neurobiological pathways are more likely to experience depressive symptoms, and therefore, antihypertensive agents targeting these pathways will also show some benefit against depression.

7.5.5 **Conclusion**

Overall, my findings support the notion that different antihypertensive classes may have distinct effects on depression risk. The results revealed that, compared with ACEI, there is a class effect of other antihypertensives on the risk of depression and that the highest negative effect was for CCB—specifically, the dihydropyridine subclass. ACEI and ARB might not be equivalent in the context of

depression. It should be emphasised that these findings may not be generalisable to other more normotensive population or those who have less severe hypertension. Further, they should be considered as preliminary evidence and future research is needed.

8 General discussion and prospects

This chapter summarises the main findings and conclusions of this thesis, and addresses strengths and limitations, clinical implications and implications for future research.

This thesis aimed to investigate the following:

1- The association between depression and risk of major subtypes of CVD (including CHD, stroke and HF), and

2- the association between exposure to antihypertensive drugs and risk of depression as indicated by the first-ever prescription of antidepressants.

8.1 Depression and risk of CVD

The first objective of this thesis was to investigate the association between depression and three CVD subtypes: CHD, stroke and HF. I considered three hypotheses that potentially could further substantiate the principle that depression should be considered a major risk factor for CVD, similar to hypertension, hyperlipidaemia, diabetes and smoking: (1) depression increases the risk of different CVD outcomes independent of pre-existing CVD; (2) depression increases the risk of CVD in a dose-response manner; and (3) baseline depression predicts future CVD events as much as time-varying depression. The study design used in this thesis to test these hypotheses was based on a systematic review and a meta-analysis.

8.1.1 Summary of the main findings

Figure 8-1 summarise main findings of the systematic review and meta-analysis study.

Chapter 3 presented the methodological quality of the included studies and main methodological considerations relating to depressive symptoms screening tools and covariates selection. Overall, 60% of the included studies were evaluated as good, while the remaining were evaluated as fair. Section 8.1.1.1 discusses methodological issues of the included studies in more detail.

In Chapter 4, I examined the impact of depression on first-ever stroke in patients with no known history of stroke or CHD at baseline. I demonstrated that depression was associated with a 22% increased risk of first-ever stroke based on 19 studies. The estimated risk for time-varying depression was 27%, confirming the significant risk of baseline depressive symptoms. I also showed that age could be a potential modifier of the association linking depression to stroke.

In Chapter 5, I examined 23 studies to evaluate the association between depression and CHD. I showed that patients who were depressed but had no CHD event or stroke before study initiation had a 22% increased risk of developing a first-ever CHD event, compared to patients who were not depressed. This estimated risk was slightly higher for patients with MI and angina (24% and 57%, respectively). Depression remains a strong predictor for future CHD events when it is modelled as a time-varying variable. I observed that the risk for future CHD was more pronounced for clinical depression than for depressive symptoms (26% vs 17%). There was some evidence that women with depression may have a higher risk of CHD than men with depression.

In Chapter 6, I examined the association between depression and incident HF in patients with no known history of CVD at baseline. Only four studies were available to compute an effect size. I found that depression was associated with a 17% increased risk of HF. To my knowledge, this review is the first to assess whether depression is associated with increased risk of HF in the absence of other CVD history. The two other hypotheses, including the effect of time-varying depression and an assessment of dose-response relationships, could not be tested due to the small number of studies.

Altogether, the current thesis provided evidence that depression associated with ~20% increased risk of developing stroke, CHD and HF in apparently healthy individuals.

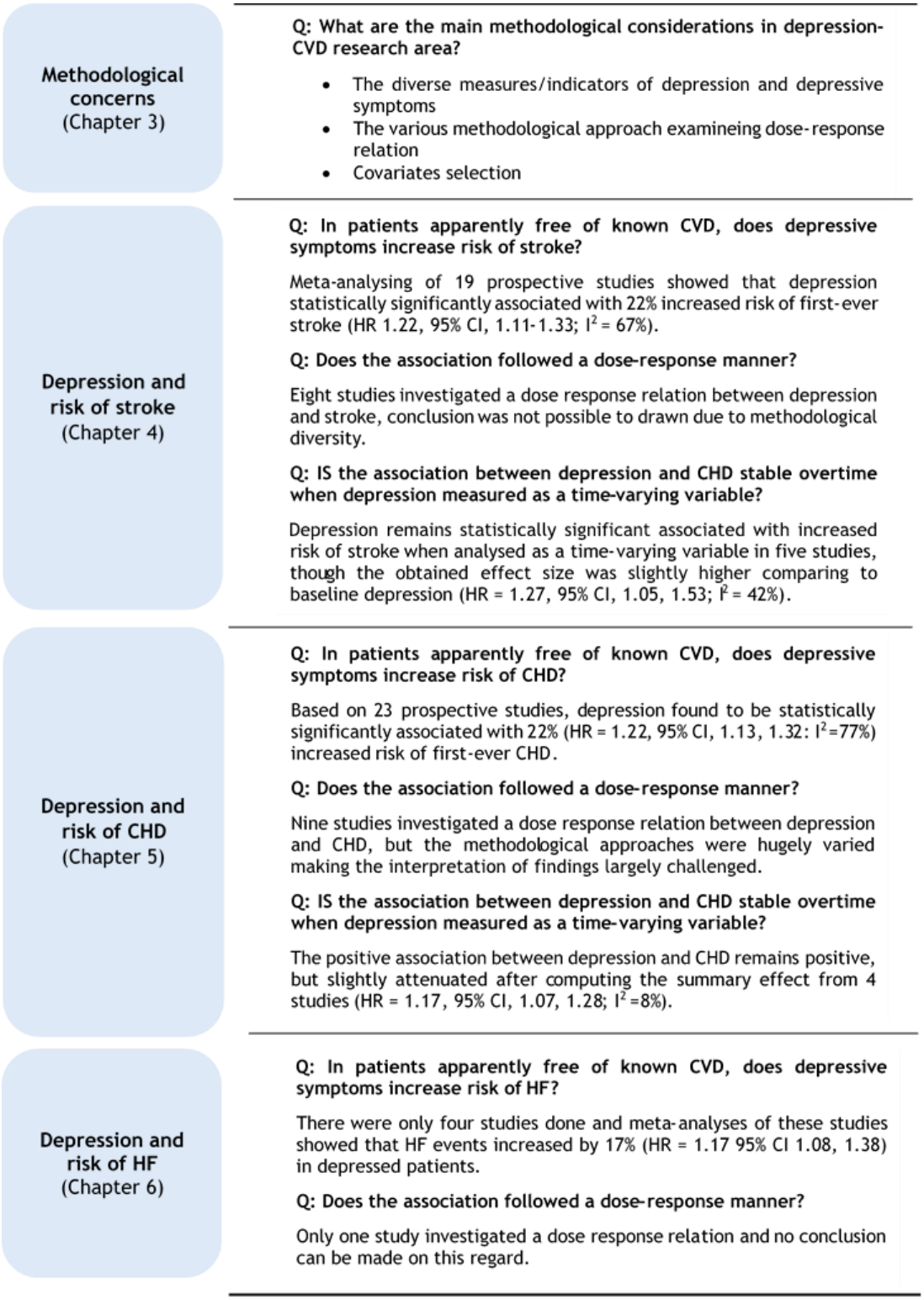

Figure 8-1 Summary of the systematic review key findings

8.1.1.1 **Methodological considerations**

In Chapter 3, I highlighted several methodological issues relating to depression screening and adjusting for covariates. Regarding depression screening, the various scales for depressive symptom screening differ in two important points. The first is that different screening scales capture depressive symptoms over different timeframes. Scales that asked about depressive symptoms experienced over the last month would obviously capture a greater duration of symptoms than those with a timeframe of one day, or one or two weeks, and it is unknown to what extent this could affect the magnitude or direction of the depression-CVD associations. The second point is that different screening scales differ in terms of the number of depressive symptoms representing each dimension of depression; some scales predominantly focus on specific dimensions of depression and exclude others. Evidence from epidemiological studies suggested that distinct type of depressive symptoms reflect the severity of depression status (Tolentino and Schmidt, 2018). Further, studies conducted among cardiac patients suggests that each dimension of depression is associated with a distinct effect on cardiac prognosis. A systematic review of 13 prospective studies with 11,128 subjects showed that the somatic symptom dimension, but not the cognitive symptom dimension, is independently associated with poor cardiac prognosis (HR = 1.19, 95% CI, 1.10-1.29) (de Miranda Azevedo et al., 2014). More recently, Norton et al. (2020) found that both symptom dimensions (i.e. somatic and cognitive) are strong predictors of new cardiac events among heart disease patients. Norton et al. (2020) also suggested that specific symptoms within the somatic dimension, such as poor appetite/overeating and feeling like a failure for the cognitive dimension, are significantly associated with the main outcome. Whether the same cluster of symptoms can also be considered predictors for incident CVD in CVD-free participants has yet to be discovered. Overall, examining the association between n depression dimensions or specific depressive symptoms and a new-onset CVD event in CVD-free patients is a relatively new approach (compared to depression in a CVD population) that has rarely been considered in past studies. To the best of my knowledge, Li et al. (2019) was one of the first studies to prospectively investigate the impact of each individual's depressive symptoms on CVD incidence among CVD-free patients. Li et al. (2019) assessed the association between 10 depressive symptoms, identified using the 10-item CES-D scale, and incidence of CVD. Of the 10 symptoms, they found that restless sleep and loneliness were the

most significant predictors for future CVD events. However, given that the main outcomes were a composite endpoint and the targeted population in this study was elderly participants, their results may not fully generalise to individual CVD subtypes or to younger adults, and thus merit further investigation. Future studies should apply multiple measurements targeting the different dimensions of depression. Their findings will help clinical practice to assess depressive symptoms, giving special attention to specific symptoms to predict and prevent future CVD-related events (Norton et al., 2020).

In Chapters 4 and 5, I identified other methodological challenges concerning the interpretation of inconsistent findings as a result of using different methods to measure depression. In the current review, depression cases were identified using different indicators, including SRS, clinical diagnosis and antidepressant prescriptions. It is plausible to expect that different depression indictors might give consistent results in terms of the direction of the associations in the context of depression and CVD incidence. A common measure of clinical depression involves combining participants receiving antidepressant treatment with those diagnosed with depression based on structured interviews to represent the depressed cohort. However, given that antidepressant medications have other clinical indications (plus the possibility that participants receiving antidepressants could have better treated depression), it is problematic to combine those patients in the depressed cohort; thus, a separate analysis to examine the impact of exposure to antidepressants on CVD incidence should be considered.

The final methodological issue concerns examining a dose-response relationship between depression and CVD incidence. Researchers investigating the depression-CVD field of research have been encouraged to investigate this aspect (Carney and Freedland, 2017, Rugulies, 2002). Although many studies have investigated a dose-response relationship, two principal challenges hindered the practicality of conducting a meta-analysis. First, the cohorts used various parameters/indications for a ‘dose of depression’ which were dissimilar enough to reduce the consistency of their research findings and preclude drawing a general conclusion. The various indications/parameters for a dose of depression that were identified in this thesis include the following: number of depressive symptoms, level of depression severity, number of cumulative episodes, number of outpatients visits due to depression and responsiveness to antidepressant

treatment. Second, the cohorts tended to use different statistical approaches when generating levels of severity, for example, based on quintiles, tertiles, standardised cut-off scores or standard deviations. One potential reason for these methodological inconsistencies is that until recently there has been no clear consensus regarding the optimal approach to examining dose-response relationships. Guidance is lacking on how to evaluate and address this and provide a standardised strategy that directs researchers to a better application of different measures of depression severity.

Table 8-1 summarises the methodological concerns and suggestions.

Table 8-1Summary of main methodological considerations within included cohorts

Main methodological issues	Suggestion	
The diverse measures/indicators of depression and depressive symptoms	**A-** Different formats of standardised screening tools	• Report the rationale of using the selected screening tool. • Describe the tool performance to measure depression, tool contents, such as type of symptoms, and the timeframe of the asked questions. • Standardise the timeframe of the asked question. • Consider using the optimal cut-off score (when depression is categorised as a binary variable) based on the best available evidence. • Apply multiple measurements targeting the different dimensions of depression and investigate the relation between each dimension and CVD outcomes.
	B- Combined indicators (e.g. antidepressants with MDD)	• Perform a sensitivity analysis excluding antidepressants users. • Calculate the risk estimate of a CVD event for each examined indicator. • Extract sufficient information when examining antidepressants as a proxy of depression, such as the type of antidepressant, doses and duration of exposure.
The diverse measures/indicators for dose-response relation	A- Indication for a dose of depression	• Apply multiple measurements to allow for direct empirical comparisons and enhance understanding of the fundamental differences between different measures of a dose-response relation with respect to CVD outcome.[(a)] • Different studies may consider adopting similar approaches based on previous compelling evidence and use of a comparable screening tool. • Measure depressive symptoms at multiple instants over the follow-up period and model depression as a time-varying variable • Consider analysing patterns of depressive symptoms over the follow-up period, such as previous history, new onset episode, duration of the depressive episode, persistent, remitted and stable.
	B- Statistical methodology to generate different levels of severity	• Consider multiple statistical approaches to derive increasing levels of severity (e.g. based on standard deviation and tertiles). • Consider analysing depression as a continuous variable and as a binary variable simultaneously.

CVD, cardiovascular diseases; [a]Modified from (Rutledge and Goulda, 2019)

8.1.2 **Strength of the review**

This review integrates study findings included in prior reviews with findings from the most recent prospective studies, resulting in an extremely large sample size and thus providing greater reliability (precision) of the estimated effects. This review was strict about including only studies that enrolled participants who were free of CHD and stroke histories at study initiation, which to some extent reduced the between-studies variation in terms of the baseline risk of developing CVD. This requirement implied that my results were unaffected by pre-existing clinically apparent CHD or stroke events and, therefore, findings are robust to conclude that depression is associated with an increased risk of CVD incidence, independent of previous or coexisting cardiac or stroke events. This review also examined the association between depression and three subtypes of CVD rather than focusing on a single CVD outcome. Further, I performed a meta-analysis from 14 studies that investigated the independent association between depression and CHD and depression and stroke simultaneously within the same population. Pooling of HR for CHD and stroke from these studies showed that depression raises the risk of developing CHD and stroke to approximately the same level (the corresponding HRs are 1.22 and 1.24), which supports the primary findings of the present review. Finally, unlike past reviews, I not only computed a summary effect size, but I also shed light on some methodological issues related to depression measures and provided suggestions that need to be considered in future epidemiological studies.

8.1.3 **Limitation of the review**

Several limitations of this meta-analysis should be considered. First, the search strategy of my review covers four databases: MEDLINE, Embase, Web of Science and PsycINFO. However, despite Bramer et al. (2017) recommendation, I did not use Google Scholar in addition to these four databases to ensure an efficient coverage of systematic reviews. Additionally, due to the massive volume of citations generated from the four databases and time constraints, I did not search for grey literature. Nonetheless, my search covered all studies included in the latest reviews (Barlinn et al., 2015, Gan et al., 2014, Li et al., 2015a, Wu and Kling, 2016) that were published after 2004. Further, I used a wider variety of search terms compared to previous reviews. Moreover, where possible, I contacted the primary or secondary author of the respective studies, although not

many responded. I also considered abstracts if they contained the required information. Although abstracts may affect the precision of the estimated effect, I performed a sensitivity analysis excluding abstract study and results were consistent with the primary analysis. Second, my eligibility criteria were limited to a particular period (i.e. after 2004) and to studies published in English. Third, I only included studies that measured depression as a binary variable where patients should be dichotomised as 'with or without depression/depressive symptomatology' and excluded studies that measured depression as a continuous variable. Although this is likely to generate more homogenous results, there are some caveats regarding a binary measure of depression. According to Zigmond and Snaith (1983), in general, psychiatric disorders cannot be considered as either 'present' or 'absent' as the degree of distress is continuously distributed in the population. They proposed that measuring 'how much depressive symptoms' would be more relevant than measuring their presence or absence. Therefore, studies that measured depressive symptoms as a continuous variable may be closer to clinical reality than those that provided dichotomous measures. In addition, binary measures tend to conceal any linear relationship between the variable and the outcome (Altman and Royston, 2006). In the current context, this means that depression severity was not considered by studies that measured depression as a binary variable. Establishing a relationship between depression severity and CVD will provide a solid evidence base so that depression can be compared easily with the classical risk factors of CVD. Fourth, because in some cases there is no known recognised cut-off point for a certain SRS, one of the undesirable methodological consequences is that researchers are compelled to derive arbitrary cut-off points to dichotomise patients. In these cases, the results may not be generalisable to other populations. However, in the present review, relatively few studies (n = 2) adopted this approach, and the majority used a common or an optimal cut-off score to identify patients with depressive symptomatology. Fifth, the majority of studies included in this review were not designed to evaluate a dose-response relationship between depression and CVD outcomes. Additionally, even the few studies that provided such information used diverse methods to examine a dose-response relationship, which hampered meta-analysis of their findings. Finally, the functional limitation of the software used for this review. RevMan, is not built to run certain analyses. For example, investigating the possible risk of publication bias in RevMan can only be done via a visual inspection of the funnel plot, since

other statistical methods such as Eager test or trim-fill method are not supported. Furthermore, meta-regression analysis, which enables the investigation of the influence of modifiers or covariates on the effect size, is not implemented in RevMan. However, in any case, this kind of test was not a good option for my analysis because meta-regression requires a minimum of 10 studies for each covariate to produce reliable results (Higgins and Green, 2011) and I included fewer studies for each possible modifier. On balance, the subgroup analyses that I conducted in this study should meet my requirements to assess the modifier variables.

8.2 Antihypertensive drugs and risk of depression

8.2.1 Summary of the main findings

In Chapter 7, I investigated the association between antihypertensive drugs and the risk of incident depression by applying different study designs. Findings emerging from these studies were consistent, showing that among the five drug classes, CCB, in particular dihydropyridine, is associated with an increased risk of incident depression compared to ACEI. I also explored a dose-response relationship between the cDDD of antihypertensive drugs and depression and showed that higher doses of ARB therapy were marginally associated with the risk of incident depression.

8.2.2 Study strengths and limitations of the GBPC cohort

The main strengths of the GBPC cohort study include the large cohort size conducted in real-life settings with global healthcare records obtained through the electronic linkage; long duration of follow-up; large number of events; and availability of refill prescription data. My study has further expanded the previous work based on recommendations from the latest research. It also gained an advantage over past studies in terms of the multiple study designs that were used to investigate the antihypertensive-depression relationship. The study's main objectives were not limited to detecting the class of antihypertensive medications associated with depression, but also providing information on a dose-response relationship between antihypertensive medications and depression. Furthermore, the design of the monotherapy cohort study created a fixed period of exposure (i.e., one year), standardising the exposure duration for all study participants. I

also provided risk estimates for ARB and ACEI separately, which has rarely been considered in prior studies. Further, I limited the monotherapy analysis to participants without a history of CVD and excluded those who developed CVD during the exposure period and obtained a consistent risk estimate, suggesting that confounding due to CVD as an indication for antihypertensive treatment did not alter the aggregate findings. Finally, although the data were derived from one population, two different study designs and analyses were used and results were very similar serving to increase the internal and external validity of the findings.

There are, however, several limitations that should be considered. The observational design precludes us from drawing conclusions regarding causality between antihypertensive medications and depression. A primary disadvantage of the GBPC cohort is that I was unable to examine an "antihypertensives-free" cohort and follow them up prospectively to compare depression outcomes between patients who were treated with antihypertensives and those who were not. Furthermore, patients in the GBPC cohort were confined to secondary and tertiary care hypertension clinic in the West of Scotland. Thus, my results may not be generalisable to other apparently healthy normotensive populations, or indeed less severely hypertensive patients. Residual confounders may provide an alternative explanation. For example, particpants in the GBPC are likely to have resistance hypertension, being multimorbid and have family history of CVD. Although I adjusted for the CCI, which has been widely used in clinical practice to adjust for comorbidities, it has been suggested that this confounding tool may be insufficient to control for comorbidities. As a result, relying solely on the CCI may result in considerable residual confounding (Renson and Bjurlin, 2019), and therefore biased results and conclusions. Another example is the socioeconomic status of particpants. The GBPC study has no data on the socioeconomic status of the included participants, so I was unable to adjust for this variable in the analysis. The association between socioeconomic status and depression is well documented by several studies (Freeman et al., 2016, Lorant et al., 2007, Lorant et al., 2003). Lockhart and Guthrie (2011) conducted a prospective cohort study to examine the prescribing pattern of antidepressants in a primary care facility in the Tayside region of Scotland. The study measured the socioeconomic status for patients using the postcode-assigned Scottish Index of Multiple Deprivation (SIMD), which was divided into quintiles, with the first quintile representing the least deprived

area and the fifth quantile representing the most deprived area. The study found no consistent gradient of either antidepressant use or increases in antidepressant use by the SIMD. Additionally, increased prescribed use of antidepressants was experienced by all socioeconomic groups. Perhaps this may indicate that the socioeconomic factors may explain only a small proportion of the association in this population, including the population of this study.

It is important to emphasise that confounding by indication is difficult or even impossible to avoid in pharmaco-epidemiological work. This is one of the key confounders in this study for two reasons. First, my population is hypertensive, which could be the primary trigger of depression. Second, the diverse indications of antihypertensive medications include cardiac indications. This is problematic when investigating the association between antihypertensive medications and depression in a population with established CVD, as it is very likely that the result could be confounded by the cardiovascular indication of antihypertensive drugs. However, as aforementioned, I excluded patients with a history of CVD, and the results were unchanged. Further, in the monotherapy analysis, the mean age of patients started on CCB was 52 years, which is below the recommended age to initiate CCB (55 years) according to the hypertension guidelines. This may indicate that those patients treated with CCB had more severe cardiac conditions than patients treated with ACEI. As a consequence, the significant association observed between CCB and incident depression may reflect CVD severity at baseline. However, this problem of sequencing was overcome in the polytherapy analysis, and findings from both analyses were consistent. Nevertheless, given that

In the monotherapy analysis, the main “exposure” (i.e., antihypertensive medication) was not measured as a time-varying variable. Patients with hypertension often require multiple medications, switching medications and titrating the doses to control their hypertension. Cox proportional analysis based only on baseline measures would mean that I used a very limited part of the information that is contained in the history of using certain antihypertensive drugs and thereby introduced a bias (Stricker and Stijnen, 2010). Moreover, the DDD was categorised into three groups based on tertiles and the comparison was performed between the lowest and the highest tertile of DDD. The cut-off points for these groups are statistically driven and may have little clinical meaning.

Depression cases were identified using prescription data of antidepressants from the ISD; however, additional information about what actual conditions antidepressants have been prescribed for was not available. Antidepressant medications are known to be used for other conditions with proven benefits, such as chronic pain.. The ISD annual report, "Prescribing in Mental Health," provides summary information on antidepressant use in Scottish Health Boards during the period 2003/04 up to 2012/13 (Information Service Division, 2013), which is compatible with the follow-up period in the GBPC cohort. It was reported that the number of prescriptions dispensed for low doses of amitriptyline tablets (a TCA medication) increased from 26.4% of dispensed items in 2003/04 to 49.8% by 2012/13, whereas prescription of higher doses of amitriptyline tablets declined from 46.9% to 31.2% of dispensed items. According to the prescribing guidance of the British National Formulary, lower doses of amitriptyline are not recommended for treating depression; instead, they are being used to treat a range of largely unlicensed but recommended indications, such as neuropathic pain and migraine prophylaxis (Information Service Division, 2013). Based on this information, it can be inferred that a change in practice has occurred with amitriptyline being used to treat indications other than depression (Information Service Division, 2013). Therefore, it is very likely that the current study suffers from bias due to misclassification of the outcome, although the extent to which it affects my results cannot be determined. Besides, I showed in the meta-analysis chapters (4 and 5) that antidepressants may not be a reliable proxy to identify depressed cases and results could vary if depression measured using clinical diagnostic criteria.

The aim of this cohort study was to investigate whether there was an association between exposure to different antihypertensive medications and depression. Approximately more than 75% of the population had received antihypertensive treatment for less than or equal to six months during the exposure period. This might indicate that those patients had poor adherence behaviour. Alternatively, given that the time window for the exposure duration in the current study is relatively short (i.e., only one year), the initial therapeutic plan for those patients might have been for short-term treatment only. Shaw et al. (2019) suggested that the effect of antihypertensive medications on MDD is likely to vary with time. Another cross-sectional study proposed that initiation of antihypertensive medication in newly diagnosed hypertensive patients significantly improved

depression and other psychological scores after three months of treatment (Korosi et al., 2017). These findings suggest that the effect of antihypertensives may indeed vary with time and, perhaps, that there is a therapeutic (or harmful) window, depending on the dose or the length of the exposure. Accordingly, the results obtained from this study may not be an accurate reflection of the actual effect of antihypertensive medication over a one-year period.

8.2.3 **Clinical implications**

8.2.3.1 **Depression and CVD**

Patients with depression are at a considerable risk of developing CVD, particularly CHD, stroke and HF (likely 1 in 5 will develop CVD) in the absence of a known history of a CVD event. The risk imposed by depression on CVD might be similar to a transient episode of depression with minor symptoms and with cumulative severe episodes. Detecting depression is not as easy a task as identifying other major risk factors of CVD, such as hypertension or diabetes. Therefore, it is important that clinicians increase their efforts to detect depression in its early phase, as the impact and consequences of depression onset might be more severe in some groups of patients, including adults at young and middle ages (< 65 years) and women.

8.2.3.2 **Hypertension, antihypertensive drugs and depression**

Elevated BP is the most important modifiable risk factor for premature death worldwide. There are multiple drugs available for the treatment of high BP and the effect of these drugs on mortality and incident CVD has been evaluated in numerous RCTs and summarised in several systematic reviews and meta-analyses. All major systematic reviews agree that antihypertensive treatment is associated with reduced risk of death and CVD for an SBP of 140 mm Hg or higher and all guidelines recommend commencing these patients on treatment. In this context, if antihypertensive therapy induces depression it will have an adverse impact on hypertension control as depression, especially unrecognised depression may have a major impact on antihypertensive drug adherence and BP control with a detrimental effect on cardiovascular risk and mortality. Thus, understanding the impact of antihypertensive therapy on depression is crucial both from a public

health perspective in reducing the population burden of CVD and also from the patient perspective with the adverse impact on depression on quality of life.

My findings suggest that dihydropyridine CCB drugs may place hypertensive patients at a greater risk of developing depression compared to ACEI drugs, although the generalisability of this finding may be limited to a high-risk CVD population. As recommended by the current guidelines for hypertension treatment and CVD prevention, CCB is one of the initial drugs that should be used to manage hypertension, making the prescription of these medications highly prevalent. Therefore, despite the limited generalisability of the current findings, it is important that clinicians are aware of possible neuropsychiatric adverse events of CCBs. They may need to evaluate mental health while prescribing CCB to hypertensive patients, particularly those with established CVD. This is primarily because depression in such patients becomes an important factor that requires routine screening to prevent any negative impact on quality of life and possible gains in morbidity and mortality. Furthermore, the current study proposed that high doses of ARB may make patients more susceptible to developing depression. While this finding should be considered preliminary evidence that merits further investigation, it suggests that evaluation of the patient's mental health at each stage of dose titration may have to be considered, and adjustment of the dosage regimen should be made if medication adverse effects in mood are suspected. Guidelines on hypertension management should also consider neuropsychiatric side effects of antihypertensive drugs and alternative treatments in those at high risk of depression. Lastly, as the diagnosis of depression may not be easy or straightforward in physically ill patients, patients treated with antihypertensive drugs should be encouraged to report depression-related symptoms even if they think, from their perspective, that they stem from physical discomfort.

8.2.4 **Implication for future research**

It has been two decades since the first systematic review was published revealing a positive association between depression and a single CVD subtypes (Rugulies, 2002). The first review was followed by 10 reviews, including my study. Nevertheless, despite the observed improvement in the precision of the estimated risk of depression, additional new science to the literature provided by these reviews does not go beyond quantifying an effect size of depression risk as a single

diagnostic entity. The inability of systematic reviews to further expand the knowledge base on depression-CVD relationships indicates a paucity of new primary research in this area. Future studies should examine the dynamic aspects of depressive symptoms over the follow-up period relating to CVD and subclinical CVD. In the following section, I outline some research gaps that need to be addressed by future studies based on the findings presented in this thesis and regarding what I have identified in the literature through reviewing studies for eligibility.

8.2.4.1 **Remission/Previous history**

The majority of studies that established a relationship between depression and CVD incidence relied on a single baseline measurement of depression, which reflects an active (i.e. ongoing) or a new onset episode. In the current evidence base, it is not clear whether a previous history or a remitted depressive episode would carry the same risk on CVD outcomes as a baseline status of depressive symptoms. Few studies in the literature have examined such a possibility, and where this has been done the findings are inconsistent. For example, Pan et al. (2011a) in the Nurses' Health Study cohort showed that women who reported a current depression episode had a 41% increased risk of developing a stroke (HR = 1.41, 95% CI, 1.18, 1.67), while those who only had a past history of depression were at a non-significant elevated risk (HR = 1.23, 95% CI, 0.97–1.56). However, Daskalopoulou et al. (2016) found that the risk of developing CVD was similar for a previous history and new onset depression. Remission of depressive symptoms has been proposed as a potential predictor of lower incidents of second cardiac events and mortality in post hoc analyses of RCTs that investigated the impact of depression treatment on poor prognoses in cardiac patients (see Section 1.1.7). In light of this evidence, it would be expected that in a CVD-free patient, a past depressive episode that was completely remitted is not associated with an elevated risk of developing CVD. However, the opposite could be also possible where the pathological consequences stimulated by one depressive episode might persist regardless of the episode going into a remission status through treatment (Baune et al., 2012). However, limited evidence in the literature is available to support either notion.

Seldenrijk et al. (2015) investigated six-year associations between depression and newly developed CVD in 2,510 CVD-free participants in the Netherlands Study of Depression and Anxiety. The investigators found that compared to non-depressed participants, patients with current or remitted depression did not have an increased risk of developing a new CVD event. By contrast, Gilsanz et al. (2015) recruited 16,178 participants from the Health and Retirement Study, who were free from stroke at study entry and showed that a new-onset depressive episode is not associated with increased risk of developing stroke over a four year of follow-up, unlike a remitted episode which was associated with a 66% increased risk of stroke incident (HR = 1.66, 95% CI, 1.22, 2.26). More recently, Gilsanz et al. (2017) suggested that neither a new-onset nor a remitted depressive episode is associated with incident stroke during the year following two consecutive annual assessments of depressive symptoms. Notably, the two later studies examined stroke outcomes over a relatively short period, which restricted their findings.

Further, other factors should be considered when studying depression remission. For example, whether the remitted episode was treated or untreated and, if it was treated, whether the intervention was introduced at an early phase or at an advanced phase of the episode, identifying how each could affect the development of CVD outcomes. It is not uncommon that participants may remit before receiving an intervention, and this period could last up to a year. In a systematic review of 19 studies, Whiteford et al. (2013) investigated the proportion of prevalent cases of untreated major depression that will remit without treatment in a year and examined whether remission rates vary by disorder severity. Untreated depressed cases were drawn from consenting wait-list and primary-care samples. Depression in this study was identified based on either clinical diagnosis or cases that exceeded the thresholds score on a standardised SRS (Whiteford et al., 2013). The main findings were that 23% of untreated depressed patients remitted within three months, 32% within six months and 53% within 12 months. An inverse association between remission rate and severity was also reported (Whiteford et al., 2013). Another study showed that 62% of patients with MDD were found to be still depressed after five months from the baseline assessment, suggesting that depression cannot in all cases be considered a self-limiting disorder (Penninx et al., 2001). The pathological damage that is imposed by depression if untreated could occur before symptoms are

completely remitted and is in some cases irreversible (e.g. early onset depression [patients ≤ 21 years]) (Schmaal et al., 2016). Another factor that may also be considered is the duration of an episode. Epidemiological data have shown that the probability of recovery from an episode declines with increasing episode duration (Patten, 2006). This factor might also be considered a possible measure to determine a dose-response relationship between depression and CVD.

Future research on how changes in depressive symptoms influence CVD-related outcomes should consider whether any significant differences exist between different lengths of depressive episode duration, treated and untreated previous, but dormant, history of depressive episode and whether the timing of medical intervention modifies the relation. An RCT is the ideal study design to answer these questions; however, due to ethical constraints preventing randomising depressed participants to remain untreated, observational studies should be considered.

8.2.4.2 **Relapse/Recurrence**

A relapse or recurrence of depression could be an important sign of a distinct biological profile of a MDD subtype. Patients experiencing recurrent depressive episodes may strongly deviate from healthy individuals in terms of the pathophysiological and genetic aspects (Lok, 2013). Schmaal et al. (2016) demonstrated that the morphological structures of the brain can be potentially changed in a detrimental way with depression recurrence, which may also be a sign of severity. In relation to CVD, few past studies have included this patient group, though findings from these studies were consistent, suggesting that a history of recurrent depression, but not a single lifetime of a depressive episode, is associated with increased risk of subclinical CVD and CVD events (Jones et al., 2003, Seldenrijk et al., 2015, Wagner et al., 2009, Windle and Windle, 2013). However, most literature in this area is significantly limited by the paucity of prospective studies and by studies targeting a selected group of the population. Future studies aiming to investigate a dose-response relation could consider measuring recurrent depression as a proxy for depression severity. It would also be worth examining whether any pleiotropic genetic variants contribute to both major recurrent depression and CVD.

8.2.4.3 Depression subtype and risk of incident CVD

Most studies in the literature examined depression as a single diagnostic entity irrespective of its subtypes (Baune et al., 2012). However, it remains unclear whether there are any depression subtype-specific associations. In a comprehensive systematic review, Baune et al. (2012) examined possible biological mechanisms implicated in the association between depression and CVD. The authors suggested that different depression subtypes may increase the risk of developing CVD via distinct biological mechanisms such as immune activation and HPA axis hyperactivation, which could also explain the differences in the strength of the associations between specific subtypes of depression and CVD. To my knowledge, only two studies were published between 2005 and 2020 investigating the longitudinal association between depression subtypes and the incidence of CVD. The first study, which was carried out by Case et al. (2018), enrolled 28,726 adults who were initially free of CVD. The authors examined the risk associated with MDD, typical depression, atypical depression, dysthymia and double depression (defined as a history of both lifetime dysthymic disorder and MDD) compared to a control group with no known history of depression. The findings showed that compared to the control group, all depression subtypes had a statistically significant association with incident CVD; however, the odds of incident CVD were more pronounced for atypical depression (OR = 2.19, 95% CI, 1.71, 2.81) and double depression (OR = 2.17, 95% CI, 1.92, 2.45). Other studies in the literature examining the cross-sectional association between atypical depression and prevalent CVD reported inconsistent findings (Brailean et al., 2020, Niranjan et al., 2012, Vogelzangs et al., 2010), which merits further exploration.

The second prospective study was conducted more recently by Rantanen et al. (2020a) among 2,522 patients with elevated CVD risk. The authors classified the patients into three groups, including subjects with and without non-melancholic depressive symptoms and a control group of subjects with no depressive symptoms. Compared to the control group, only non-melancholic depressive symptoms were found to be strong predictors of CVD incidents (IRR = 1.69, 95% CI, 1.23, 2.31). The authors further stratified the analysis based on CVD subtypes, and the results remained statistically significant with CHD, stroke and PVD. This is a useful avenue for further research assessing depressive subtypes in relation to different CVD subtypes. Future research should thus take into consideration

possible biological and genetic mechanisms that might be involved in the pathological pathways to enhance clinical services to detect, treat and prevent premature CVD.

8.2.4.4 The effect of antidepressant treatment on incident/ complication of CVD

As previously described in the introduction (see section 1.1.7), the effect of antidepressants on CVD is still a controversial issue. There is huge uncertainty about how antidepressant can influence CVD. Evidence are mixed showing both negative and positive results. Despite the optimistic findings that were recently published by Kim et al. (2018) and Lavoie et al. (2018), which showed that antidepressants may be cardio-protective, there are also several pre-clinical reports revealing that certain drugs within the SSRI, first-line antidepressants drug class, can promote the pathophysiological cascade of CVD development (Rami et al., 2018, Shively et al., 2015, Ungvari et al., 2019). The later could partly justify the failure of several RCTs to report any significant risk reduction toward CVD endpoint, despite the noticeable improvement in depressive symptoms as treated by antidepressants (Berkman et al., 2003, Glassman et al., 2002a, van Melle et al., 2007, Zuidersma et al., 2013). Future studies should prospectively evaluate the association between antidepressants drugs, particularly the first line medications, and subclinical endpoints of CVD. Further, because the association between depression and CVD is currently well established, discovery of new treatment that can target the complex interplay between these disorders might be valuable in clinical practice as a new therapeutic approach.

8.2.4.5 Antihypertensive drugs and depression

At present, the available evidence examining iatrogenic depression as a consequence of antihypertensive drugs is limited to the incidence of depression. If depression is an adverse drug reaction of certain medications, then it is plausible to expect recurrent episodes of depression with the continuous use of these medications. Therefore, future studies with long-term follow-up exploring the trajectory of depressive symptoms among antihypertensive drug users are needed. These could also be done with the aid of technology, whereby patients can be advised to self-report depressive symptoms over scheduled secessions, which can enhance the number of observations over the follow-up period and ensure that

different levels of depressive symptom severity are captured. Moreover, most of the previous studies on the association between antihypertensive drugs and incident depression compared antihypertensive drug users with non-users (or with short-term users). This approach makes it difficult to separate the effect on depression risk of antihypertensive drugs from the effect of the chronic underlying CVD condition. Future studies can minimise bias due to confounding by indication and be more specific in investigating the effect of antihypertensive drugs based on baseline CVD conditions (i.e., antihypertensive users without CVD vs. antihypertensive users with CVD). This would enable researchers to evaluate the association of antihypertensive drugs and incident depression in a subgroup of patients with normal cardiovascular health and compare the effect of antihypertensive drugs to those of patients with cardiovascular problems, as evidence suggested that the effect of treatment might be only present in patients with the condition being treated (Agustini et al., 2020). It would also be beneficial to explore whether an improvement in cardiovascular functions by antihypertensive drugs would also contribute to a reduced risk of incident depression. Lastly, because clinical judgment should be based on medical evidence obtained through robust scientific research, a well-designed RCT will be the only solution that can provide a clear answer to whether repurposing antihypertensive drugs, particularly those that have strong support from the literature such as RAS agents, would bring any significant clinical benefit in the depression context.

8.2.5 **Conclusion**

In conclusion, I investigated the association between baseline depression, time-varying depression, and the incidence of CVD outcomes within a CVD-free population. Overall, I provided robust evidence that baseline depression imposes a similar level of risk across different CVD subtypes, including CHD, stroke, and HF, independent of other major risk factors of CVD. The strong contribution of depression to first-ever HF demonstrated here within a CVD-free population should encourage researchers to investigate the biological factors involved in pathological pathways linking the two conditions. Time-varying depression was also a strong predictor for CHD and stroke incidents, although further study is warranted to verify this finding and investigate its effects in relation to HF. I also identified several important methodological issues limiting the practicality of a

meta-analysis in investigating a dose-response relationship between depression and CVD, and I provided suggestions for future epidemiological studies.

Furthermore, I investigated the association between antihypertensive drug classes and incident depression. Among the five major classes, dihydropyridine CCB therapy could carry a greater risk of incident depression compared to ACEI therapy. However, due to the overall limitation and the limited generalisability of the current study, these findings should be considered with caution and antihypertensive drugs should continue to be used by clinicians as recommended by the current guidelines for hypertension treatment and CVD prevention, bearing in mind the possible neuropsychiatric adverse effects of these drugs.

Overall, this thesis further supports the bidirectional association notion between depression and CVD. Clinicians, including cardiologists, psychiatrists, and other relevant stakeholders, such as clinical guidelines and policy writers, should make a collaborative effort to ensure the adoption of the best clinical practice for related patients with a balance between mental health, cardiac health and quality of life.

Appendices

Appendix 1: Systematic review protocol[1]

Review title	Depression associated with first incidence of cardiovascular disease (CVD): A systematic review and meta-analysis
First reviewer	Anwar Alnakhli
Review team	Prof Sandosh Padmanabhan Prof Daniel Smith Mohammed Ba-zuhair Nur Aishah Che Roos
Search strategy	• The search was applied to four databases: Medical Literature Analysis and Retrieval System Online (MEDLINE [OVID], from 2005 onwards), Excerpta Medica Database (EMBASE [OVID] from 2005 onwards), Web of Science (from 2005 onward) and Psychological Information Database (PsycINFO, from 2005 onwards). • The reference lists of the most relevant papers and reviews were searched manually to identify any relevant study not detected by the electronic search. • The search was limited to the period after 2004 and studies written in English.
Inclusion criteria	• **P**articipants: Adult population of men and women aged 18 years old and over and with no history of ischemic heart disease (IHD) or cerebrovascular disease (CBVD) at the time of study initiation. • **E**xposure: Participants diagnosed with depression, which refers to major depression, clinical depression, depressive disorder, depressive mood and depressive symptoms. A screening or diagnosis strategy for measuring depression was prospectively performed at baseline and included a standard-self repor :al diagnostic interview, and/or a physician/clinica • **C**omparator: Eligible studies are required to have a control group of participants with no depression at the time of the study initiation. • **O**utcome: First-ever CVD during the follow-up period divided into three groups, based on the 10th Revision of the International Classification of Diseases (ICD-10): (a) ischaemic heart diseases (ICD-10 code I20-I25); (b) cerebrovascular disease (stroke) (ICD-10 code I60-I69); (c) heart failure (ICD-code 150). • **S**tudy design: Prospective cohort studies.
Exclusion criteria	• Participants <18 years with history of CHD or stroke at study entry and participants diagnosed with bipolar depressive disorder. • Depression combined with other mood disorders, such as anxiety, screening or diagnostic strategy, non-specifically measured depression (e.g. measures anxiety alone or other generalised psychological distress). • CVD outcome was reported as a combined endpoint or not prespecified in the inclusion criteria. • The study had no control group of participants without depression.
Review method	• Study selection: The first reviewer (AA) conducted abstract screening and assessment of full texts. Two reviewers (MB & NC) checked 20% of the excluded studies. Uncertainty was resolved through discussions with supervisors (SP and DS). • Data extraction: Two reviewers (AA and MB) independently extracted data in detail from the eligible studies. • Data items: (1) name of the first author; (2) year of publication; (3) study location; (4) study design; (5) sample size; (6) characteristics of study population at baseline (i.e. mean age in years and percentage of males); (7) duration of follow-up; (8) definition of depression (cut-off point); (9) measurement of depression; (10) type of outcomes; (11) number of cases; (12) measurement method of the outcomes; (13) covariates that were adjusted in the multivariable analysis; and (14) most fully adjusted RR or HR with the corresponding 95% CI. • Assessment of risk of bias: AA assessed the methodological quality of potential studies by using the Newcastle-Ottawa scale for cohort studies. • Data synthesis: Statistical analysis using RevMan 5.3 for the outcomes. The model for the meta-analysis was a random-effect model or fixed-effect model if data are sufficiently homogenous. • Sensitivity and subgroup analyses: Based on previous reviews and data availability, subgroup analyses were done for the following: ➢ Participant's characteristics (i.e. age and sex) ➢ Type of assessment of depression (clinical depression and depressive symptoms), depression measure, inclusion of antidepressants. ➢ Definition of the outcome ➢ Essential characteristics of the selected studies, including subgroups stratified by the length of follow-up, adjustments of confounders
Results presentation	Flow chart, tables and forest plots

CVD, cardiovascular diseases; IHD, Ischemic heart diseases;
(1) Systematic review registered in PROSPERO available at https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=94605

Appendix 2: Methodological quality of included studies

(Brown et al., 2011)					
Quality assessment criteria			**Authors' judgement**	**Score**	**Support for judgement**
Selection (4)	**1**	Representativeness of the exposed cohort	Somewhat representative of the average in the community	*	The study focused on primary care elderly adults of men and women aged ≥60 years on urban public health
	2	Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort	*	The same cohort sample were screened for depression and then classified as depressed and non-depressed patients
	3	Ascertainment of exposure	A self-reported depression scale	0	The study used 20-item CES-D ≥16
	4	Demonstration that outcome of interest was not present at start of study	Yes	*	The study used medical records and NDI exclusion of participants with CVD diagnosis at baseline
Comparability (2)	**1**	Study controls for age/sex	Yes	*	Age, sex race, diabetes, HTN, history of smoking, cholesterol, and ideal body weight
	2	Study controls for at least 5 additional risk factors	Yes	*	
Outcome (3)	**1**	Assessment of outcome	Outcome ascertained by secure records	*	Outcome were determined using data from the National Death Index (NDI) and medical records
	2	Was follow-up long enough for outcomes to occur (≥10years)	Yes	*	Follow-up period was for 15 years
	3	Adequacy of follow up of cohorts	Follow up rate had not reported	0	No statement about attrition rate
Total				**7**	

(Brunner et al., 2014)					
Quality assessment criteria			**Authors' judgement**	**Score**	**Support for judgement**
Selection (4)	**1**	Representativeness of the exposed cohort	Cohort was somewhat representative of the average population	0	Civil servants aged 35-55 years in 20 London based department
	2	Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort	*	The same cohort sample were screened for depression and then classified as depressed and non-depressed patients
	3	Ascertainment of exposure	A self-reported depression scale	0	The study used GHQ-30 ≥ 5
	4	Demonstration that outcome of interest was not present at start of study	No	0	Data regarding baseline characteristics of included participants were extracted from other meta-analysis
Comparability (2)	**1**	Study controls for age/sex	Yes	*	Age, sex, and ethnicity
	2	Study controls for at least 5 additional risk factors	No	0	
Outcome (3)	**1**	Assessment of outcome	Outcome ascertained by secure records	*	Self-reported confirmed by using medical records, GP confirmation and death certificate
	2	Was follow-up long enough for outcomes to occur (≥10years)	Yes	*	Follow-up period was for 24 years

	3	Adequacy of follow up of cohorts	Complete follow up - all subjects accounted for	*	Follow-up was completed for 99.9%
Total				**5**	

(Daskalopoulou et al., 2016)					
Quality assessment criteria			**Authors' judgement**	**Score**	**Support for judgement**
Selection (4)	1	Representativeness of the exposed cohort	Cohort was representative of the average population	*	Cohort recruited participants from 225 general practices including men and women aged 30 years or older
	2	Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort	*	The same cohort sample were screened for depression and then classified as depressed and non-depressed patients
	3	Ascertainment of exposure	Secure record	*	Depressed participants were identified by using medical records and/ or description of anti-depressants medication
	4	Demonstration that outcome of interest was not present at start of study	Yes	*	Study used participant's medical record to exclude CVD patients at study entry
Comparability (2)	1	Study controls for age/sex	Yes	*	Age, sex, smoking, SBP, diabetes, cholesterol, and socio-economic status
	2	Study controls for at least 5 additional risk factors	Yes	*	
Outcome (3)	1	Assessment of outcome	Outcome ascertained by secure records	*	Cardiac events were identified using medical records or death certificates
	2	Was follow-up long enough for outcomes to occur (≥10years)	Yes	*	Follow-up period was for 13 years
	3	Adequacy of follow up of cohorts	Not reported	0	No statement about attrition rate
Total				**8**	

(Davidson et al., 2009)					
Quality assessment criteria			**Authors' judgement**	**Score**	**Support for judgement**
Selection (4)	1	Representativeness of the exposed cohort	Cohort was representative of the average population	*	Targeted population consisted of all noninstitutionalized adult participants aged between 18-98
	2	Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort	*	The same cohort sample were screened for depression and then classified as depressed and non-depressed patients
	3	Ascertainment of exposure	A self-reported depression scale	0	Exposure identified using 20-item CES-D ≥10
	4	Demonstration that outcome of interest was not present at start of study	Yes	*	Patients with pre-existing CVD were excluded
Comparability (2)	1	Study controls for age/sex	Yes	*	Age, gender, and Framingham risk score
	2	Study controls for at least 5 additional risk factors	Yes	*	
Outcome (3)	1	Assessment of outcome	Outcome ascertained by secure records	*	Medical records
	2	Was follow-up long enough for outcomes to occur (≥10years)	Yes	*	Follow-up was for 10 years
	3	Adequacy of follow up of cohorts	Complete follow up	*	100% completed the follow-up
Total				**8**	

(Everson-Rose et al., 2014)					
Quality assessment criteria			**Authors' judgement**	**Score**	**Support for judgement**
Selection (4)	**1**	Representativeness of the exposed cohort	Cohort was somewhat representative of the average population	*	Cohort was a population-based study men and women aged 45-85 years recruited from 6 fields centres
	2	Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort	*	The same cohort sample were screened for depression and then classified as depressed and non-depressed patients
	3	Ascertainment of exposure	A self-reported depression scale	0	The study used 20-item CES-D ≥16
	4	Demonstration that outcome of interest was not present at start of study	Yes	*	The cohort demonstrated that participants at baseline were free of any CVD by clinical examination
Comparability (2)	**1**	Study controls for age/sex	Yes	*	Age, race, sex, education and study site, systolic blood pressure, alcohol use, smoking status, moderate and vigorous physical activity, BMI, height, use of anti-hypertensives, diabetes/fasting blood glucose status, high density lipoprotein cholesterol, and triglycerides
	2	Study controls for at least 5 additional risk factors	Yes	*	
Outcome (3)	**1**	Assessment of outcome	Outcome ascertained by independent blind assessment	*	Incidence of the event was assessed by reviewing all medical records by two independent reviewers who were blinded to the study data
	2	Was follow-up long enough for outcomes to occur (≥10years)	Yes	*	Follow-up was for 12 years
	3	Adequacy of follow up of cohorts	Not reported	0	No statement about attrition rate
Total				**7**	

(Gafarov et al., 2013)					
Quality assessment criteria			**Authors' judgement**	**Score**	**Support for judgement**
Selection (4)	**1**	Representativeness of the exposed cohort	Cohort was selected group of users	0	Cohort was a random representative sample of women aged 25-64 years
	2	Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort	*	The same cohort sample were screened for depression and then classified as depressed and non-depressed patients
	3	Ascertainment of exposure	A self-reported depression scale	0	The study used 15-item MOPSY
	4	Demonstration that outcome of interest was not present at start of study	Yes	*	The cohort demonstrated that participants at baseline were free of participants at baseline were free of HTN, CBVD, MI, CAD, MI and diabetes but not reported how they were assessed at baseline
Comparability (2)	**1**	Study controls for age/sex	Yes	*	Age and sex
	2	Study controls for at least 5 additional risk factors	No	0	
Outcome (3)	**1**	Assessment of outcome	Outcome ascertained by secure records	*	Incidence of the event was confirmed by means of examination, reviewing medical records, card and death certificates
	2	Was follow-up long enough for outcomes to occur (≥10years)	Yes	*	The follow-up was for 16 years
	3	Adequacy of follow up of cohorts	Complete follow-up	*	Almost 100% completed the follow-up
Total				**6**	

(Gump et al., 2005)

Quality assessment criteria			Authors' judgement	Score	Support for judgement
Selection (4)	**1**	Representativeness of the exposed cohort	Cohort was selected group of users	0	Men who had above average risk of CHD because of high blood pressure, elevated blood cholesterol levels, and/or cigarette smoking
	2	Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort	*	The same cohort sample were screened for depression and then classified as depressed and non-depressed patients
	3	Ascertainment of exposure	A self-reported depression scale	0	Exposure identified using 20-item CES-D ≥16
	4	Demonstration that outcome of interest was not present at start of study	Yes	*	Data regarding stroke at baseline were extracted from other meta-analysis
Comparability (2)	**1**	Study controls for age/sex	Yes	*	Age, intervention group, race, educational attainment, smoking at baseline and visit 6, trial averaged SBP, alcohol consumption, and fasting cholesterol, as well as the occurrence of nonfatal cardiovascular events during the trial.
	2	Study controls for at least 5 additional risk factors	Yes	*	
Outcome (3)	**1**	Assessment of outcome	Outcome ascertained by secure records	*	National Death Index or Social Security Administration files. cause of death determined by death certificates
	2	Was follow-up long enough for outcomes to occur (≥10years)	Yes	*	Follow-up duration was for 18 years
	3	Adequacy of follow up of cohorts	Subjects lost to follow up unlikely to introduce bias	*	follow-up was for >90%
Total				**7**	

(Gustad et al., 2013)					
Quality assessment criteria			**Authors' judgement**	**Score**	**Support for judgement**
Selection (4)	**1**	Representativeness of the exposed cohort	Cohort was somewhat representative of the average population	*	Cohort was a population-based study including adult men and women
	2	Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort	*	The same cohort sample were screened for depression and then classified as depressed and non-depressed patients
	3	Ascertainment of exposure	A self-reported depression scale	0	The study used HADS-D ≥11
	4	Demonstration that outcome of interest was not present at start of study	Yes	*	Only CVD free participants at baseline were enrolled
Comparability (2)	**1**	Study controls for age/sex	Yes	*	Age, sex, marital status, education, smoking, physical activity, BMI, total cholesterol, diabetes mellitus and systolic BP
	2	Study controls for at least 5 additional risk factors	Yes	*	
Outcome (3)	**1**	Assessment of outcome	Outcome ascertained by secure records	*	Clinical diagnosis and death registry
	2	Was follow-up long enough for outcomes to occur (≥10years)	Yes	*	Follow-up was for 11.4 years
	3	Adequacy of follow up of cohorts	No	0	lost to follow-up was <28%
Total				**7**	

(Gustad et al., 2014b)					
Quality assessment criteria			**Authors' judgement**	**Score**	**Support for judgement**
Selection (4)	**1**	Representativeness of the exposed cohort	Cohort was somewhat representative of the average population	*	

	2	Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort	*	The same cohort sample were screened for depression and then classified as depressed and non-depressed patients
	3	Ascertainment of exposure	A self-reported depression scale	0	The study used HADS-D ≥11
	4	Demonstration that outcome of interest was not present at start of study	Yes	*	Authors carried additional analysis excluding patients with CVD at baseline
Comparability (2)	**1**	Study controls for age/sex	Yes	*	Age, sex, marital status, education, smoking, physical activity, BMI, total cholesterol, diabetes mellitus, resting HR, SBP, alcohol, serum creatinine, time-dependent adjustment for AMI during follow-up.
	2	Study controls for at least 5 additional risk factors	Yes	*	
Outcome (3)	**1**	Assessment of outcome	Outcome ascertained by secure records	*	Medical records
	2	Was follow-up long enough for outcomes to occur (≥10years)	Yes	*	Follow-up was for 13 years
	3	Adequacy of follow up of cohorts	No	0	lost to follow-up was <26
Total				**7**	

(Hamieh et al., 2019)					
Quality assessment criteria			**Authors' judgement**	**Score**	**Support for judgement**
Selection (4)	**1**	Representativeness of the exposed cohort	Cohort was somewhat representative of the average population	0	Middle-aged worker population
	2	Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort	*	The same cohort sample were screened for depression and then classified as depressed and non-depressed patients
	3	Ascertainment of exposure	A self-reported depression scale	0	Exposure identified using 20-item CES-D
	4	Demonstration that outcome of interest was not present at start of study	Yes	*	Only CVD free participants at baseline were enrolled
Comparability (2)	**1**	Study controls for age/sex	Yes	*	Age, sex, hypertension, diabetes, dyslipidemia, occupational grade, parental CHD history, obesity, smoking status and physical inactivity.
	2	Study controls for at least 5 additional risk factors	Yes	*	
Outcome (3)	**1**	Assessment of outcome	Outcome ascertained by secure records	*	Medical records or self-reported confirmed by medical records
	2	Was follow-up long enough for outcomes to occur (≥10years)	Yes	*	Follow-up was for 20 years
	3	Adequacy of follow up of cohorts	No	0	No statement about attrition rate
Total				**6**	

(Janszky et al., 2010)					
Quality assessment criteria			**Authors' judgement**	**Score**	**Support for judgement**
Selection (4)	**1**	Representativeness of the exposed cohort	Cohort was selected group of users	0	Participants were young men aged between 18 and 20
	2	Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort	*	The same cohort sample were screened for depression and then classified as depressed and non-depressed patients
	3	Ascertainment of exposure	Secure record	*	Depressed patients were identified through a structured interview by a psychologist according to the (ICD-8)
	4	Demonstration that outcome of interest	Yes	*	Yes, the cohort recruted only healthy young population who

		was not present at start of study			were extensively examined for somatic conditions at baseline
Comparability (2)	**1**	Study controls for age/sex	Yes	*	Smoking, body length, diabetes, systolic blood pressure, alcohol consumption, physical activity, father's occupation, family history of coronary heart disease (CHD), and geographic area
	2	Study controls for at least 5 additional risk factors	Yes	*	
Outcome (3)	**1**	Assessment of outcome	Outcome ascertained by secure records	*	Outcome information were obtained from medical records
	2	Was follow-up long enough for outcomes to occur (≥10years)	Yes	*	Follow-up was for 37 years
	3	Adequacy of follow up of cohorts	Not reported	0	Not provided a percentage for those who lost to follow-up
Total				**7**	

(Jee et al., 2019)					
Quality assessment criteria			**Authors' judgement**	**Score**	**Support for judgement**
Selection (4)	**1**	Representativeness of the exposed cohort	Cohort was representative of the average population	*	Population-based sub-sample of subjects who undertook national health screening programme provided by National Health Insurance System (NHIS)
	2	Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort	*	The same cohort sample were screened for depression and then classified as depressed and non-depressed patients
	3	Ascertainment of exposure	Medical records	*	Medical records at least one visit diagnosed according to ICD-10 or prescription of depression medication at more than three visit
	4	Demonstration that outcome of interest was not present at start of study	Yes	*	Participants were excluded from the analyses if they had a record of admission or outpatient for CVD
Comparability (2)	**1**	Study controls for age/sex	Yes	*	Age, smoking status, hypertension, hypercholesterolaemia, diabetes and chronic renal failure
	2	Study controls for at least 5 additional risk factors	Yes	*	
Outcome (3)	**1**	Assessment of outcome	Medical records	*	Medical records
	2	Was follow-up long enough for outcomes to occur (≥10years)	No	*	Follow-up duration was for a median of 8 years
	3	Adequacy of follow up of cohorts	Not reported	0	No statement about attrition rate
Total				**8**	

(Karlsen et al., 2020)					
Quality assessment criteria			**Authors' judgement**	**Score**	**Support for judgement**
Selection (4)	**1**	Representativeness of the exposed cohort	Cohort was selected group of users	0	Population were elderly men with osteoporosis
	2	Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort	*	The same cohort sample were screened for depression and then classified as depressed and non-depressed patients
	3	Ascertainment of exposure	A self-reported depression scale	0	Exposure identified using 9-item GADS ≥2
	4	Demonstration that outcome of interest was not present at start of study	Yes	*	Additional analysis was performed excluding patients with established CVD
Comparability (2)	**1**	Study controls for age/sex	Yes	*	Age, education, race/ethnicity, diabetes, antidepressant use, BMI, cholesterol/oxidised low-density lipoprotein, smoking status, drinking habit, physical activity and sleep quality
	2	Study controls for at least 5 additional risk factors	Yes	*	

Outcome (3)	**1**	Assessment of outcome	Outcome ascertained by secure records	*	Tri-annual questionnaire and/or phone conformed by medical records. Fatal event adjudicated by death certificate, hospital record or next of kin interview
	2	Was follow-up long enough for outcomes to occur (≥10years)	Yes	*	Follow-up was for 12 years
	3	Adequacy of follow up of cohorts	No	0	No statement about attrition rate
Total				**6**	

(Khambaty et al., 2016)					
Quality assessment criteria			**Authors' judgement**	**Score**	**Support for judgement**
Selection (4)	**1**	Representativeness of the exposed cohort	Cohort was selected group of users	0	Cohort enrolled HIV- infected population
	2	Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort	*	The same cohort sample were screened for depression and then classified as depressed and non-depressed patients
	3	Ascertainment of exposure	Secure record	*	Exposure identified using electronic medical records
	4	Demonstration that outcome of interest was not present at start of study	Yes	*	Participants at baseline were free of CVD defined using medical records
Comparability (2)	**1**	Study controls for age/sex	Yes	*	Age, sex, race/ethnicity, HTN, dyslipidaemia, diabetes, statin use, CD4 cell count, HIV-1 RNA level, antiretroviral therapy regimen, hepatitis C infection, renal disease, history of abuse or dependence of alcohol and cocaine, and haemoglobin level Smoking, BMI, anti-depressants
	2	Study controls for at least 5 additional risk factors	Yes	*	
Outcome (3)	**1**	Assessment of outcome	Outcome ascertained by secure records	*	Outcome identified using medical records and death certificates
	2	Was follow-up long enough for outcomes to occur (≥10years)	Yes	*	The follow-up was for 11 years
	3	Adequacy of follow up of cohorts	Not reported	0	No statement about attrition rate
Total				**7**	

(Krishnan et al., 2005)					
Quality assessment criteria			**Authors' judgement**	**Score**	**Support for judgement**
Selection (4)	**1**	Representativeness of the exposed cohort	Cohort was somewhat representative of the average population	0	Men and women who are residents in a continuing care retirement community
	2	Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort	*	The same cohort sample were screened for depression and then classified as depressed and non-depressed patients
	3	Ascertainment of exposure	A self-reported depression scale	0	Exposure identified using GDS-15 ≥6 evaluated by physician
	4	Demonstration that outcome of interest was not present at start of study	Yes	*	Participants at baseline were free of stroke and MI diagnosed by physician
Comparability (2)	**1**	Study controls for age/sex	Yes	*	Age, Sex, level of education, marital status, Mini-Mental State Examination, BMI, HTN, CHF, arterial fibrillation, diabetes, hyperlipidaemia , and smoking
	2	Study controls for at least 5 additional risk factors	Yes	*	
Outcome (3)	**1**	Assessment of outcome	Outcome ascertained by physical diagnosis	*	Outcome identified by physician diagnoses

	2	Was follow-up long enough for outcomes to occur (≥10years)	Yes	*	The follow-up was for 10 years
	3	Adequacy of follow up of cohorts	Not reported	0	No statement about attrition rate
Total				**6**	

(Ladwig et al., 2006b)					
Quality assessment criteria			**Authors' judgement**	**Score**	**Support for judgement**
Selection (4)	**1**	Representativeness of the exposed cohort	Cohort was selected group of users	*	The cohort was a population-based study of men and women with a BMI > 18.5kg/m2 who were randomly drawn from the general population
	2	Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort	*	The same cohort sample were screened for depression and then classified as depressed and non-depressed patients
	3	Ascertainment of exposure	A self-reported depression scale	0	Exposure identified using 24-item-DEEX scale
	4	Demonstration that outcome of interest was not present at start of study	Yes	*	Participants at baseline were free of stroke and MI but not reported how they were assessed at baseline
Comparability (2)	**1**	Study controls for age/sex	Yes	*	Age, total cholesterol, cigarette smoking and systolic BP, education, alcohol consumption and physical activity
	2	Study controls for at least 5 additional risk factors	Yes	*	
Outcome (3)	**1**	Assessment of outcome	Outcome ascertained by secure records	*	Outcome identified by Medical records and death certificates medical records
	2	Was follow-up long enough for outcomes to occur (≥10years)	Yes	*	The follow-up was for a maximum of 13.7 years
	3	Adequacy of follow up of cohorts	Not reported	0	No statement about attrition rate
Total				**7**	

(Li et al., 2012)					
Quality assessment criteria			**Authors' judgement**	**Score**	**Support for judgement**
Selection (4)	**1**	Representativeness of the exposed cohort	Cohort was representative of the average population	*	Patients were drawn from nationwide database
	2	Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort	*	The same cohort sample were screened for depression and then classified as depressed and non-depressed patients
	3	Ascertainment of exposure	A self-reported depression scale	*	Clinical diagnosis by psychiatrist
	4	Demonstration that outcome of interest was not present at start of study	Yes	*	All subjects who had major metabolic diseases or stroke before recruitment were excluded
Comparability (2)	**1**	Study controls for age/sex	Yes	*	Age, sex, diabetes mellitus, hypertension, hyperlipidaemia, substance comorbidities
	2	Study controls for at least 5 additional risk factors	Yes	*	
Outcome (3)	**1**	Assessment of outcome	Outcome ascertained by secure records	*	Hospital records
	2	Was follow-up long enough for outcomes to occur (≥10years)	No	*	Follow-up was for 9 years
	3	Adequacy of follow up of cohorts	Not reported	0	No statement about attrition rate
Total				**8**	

(Li et al., 2019)					
Quality assessment criteria			**Authors' judgement**	**Score**	**Support for judgement**
Selection (4)	**1**	Representativeness of the exposed cohort	Cohort was representative of the average population	*	Patients were drawn from nationwide database
	2	Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort	*	The same cohort sample were screened for depression and then classified as depressed and non-depressed patients
	3	Ascertainment of exposure	A self-reported depression scale	0	Exposure identified using 10-item CES-D ≥12
	4	Demonstration that outcome of interest was not present at start of study	Yes	*	Patient who reported stroke or heart diseases at baseline were excluded
Comparability (2)	**1**	Study controls for age/sex	Yes	*	Age, sex, residence, marital status, educational level, smoking status, drinking status, BP,BMI; history of diabetes, hypertension, dyslipidaemia, chronic kidney disease; use hypertension medications, diabetes medications, and lipid-lowering therapy
	2	Study controls for at least 5 additional risk factors	Yes	*	
Outcome (3)	**1**	Assessment of outcome	Outcome ascertained by secure records	*	Self-reported of physician diagnosis
	2	Was follow-up long enough for outcomes to occur (≥10years)	No	*	Follow-up was for 4 years
	3	Adequacy of follow up of cohorts	Not reported	0	No statement about attrition rate
Total				**7**	

(Majed et al., 2012)					
Quality assessment criteria			**Authors' judgement**	**Score**	**Support for judgement**
Selection (4)	**1**	Representativeness of the exposed cohort	Cohort was selected group of users	0	Cohort was a population-based study including only men aged 50-59 years
	2	Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort	*	The same cohort sample were screened for depression and then classified as depressed and non-depressed patients
	3	Ascertainment of exposure	A self-reported depression scale	0	Exposure identified using 13-item-modified CES-D scale
	4	Demonstration that outcome of interest was not present at start of study	Yes	*	History of stroke and CHD were confirmed by a self-administered health questionnaire and checked by trained interviewers
Comparability (2)	**1**	Study controls for age/sex	Yes	*	Age, study centres, socioeconomic factors, including marital status, education level, employment status, physical activity, smoking status, daily alcohol intake, systolic BP, use of anti-hypertensive drugs, BMI, total and high-density lipoprotein cholesterol, treatment for diabetes, and use of antidepressant
	2	Study controls for at least 5 additional risk factors	Yes	*	
Outcome (3)	**1**	Assessment of outcome	Outcome ascertained by secure records	*	Outcome identified by Medical records, death certificates and validated by 2 independent medical committees
	2	Was follow-up long enough for outcomes to occur (≥10years)	Yes	*	The follow-up was for a median of 10 years
	3	Adequacy of follow up of cohorts	Complete follow up	*	100% completed the follow-up
Total				**7**	

(Mathur et al., 2016)					
Quality assessment criteria			**Authors' judgement**	**Score**	**Support for judgement**

Selection (4)	**1**	Representativeness of the exposed cohort	Cohort was selected group of users	0	The cohort drawn from 141 general practices across the east London which is one of the most deprived in the UK
	2	Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort	*	The same cohort sample were screened for depression and then classified as depressed and non-depressed patients
	3	Ascertainment of exposure	Secure record	*	Exposure identified by viewing medical records using the diagnostic read code of depression
	4	Demonstration that outcome of interest was not present at start of study	Yes	*	Data were extracted from medical records considering patient only who were free of MI and stroke
Comparability (2)	**1**	Study controls for age/sex	Yes	*	Age, sex, and ethnic group, diabetes, hypertension, hyperlipidaemia, and smoking anti-depressant prescribing at baseline, obesity, and Townsend deprivation score, presence of co-morbid anxiety
	2	Study controls for at least 5 additional risk factors	Yes	*	
Outcome (3)	**1**	Assessment of outcome	Outcome ascertained by record linkage	*	Cardiac outcomes were defined according to the read code recorded in medical record
	2	Was follow-up long enough for outcomes to occur (≥10years)	Yes	*	The follow-up was for 10 years
	3	Adequacy of follow up of cohorts	Complete follow up	*	100% completed the follow-up
Total				**8**	

(Mejia-Lancheros et al., 2014)					
Quality assessment criteria			**Authors' judgement**	**Score**	**Support for judgement**
Selection (4)	**1**	Representativeness of the exposed cohort	Cohort was selected group of users	0	Participants were men and women aged 55-80 years at high cardiovascular risk
	2	Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort	*	The same cohort sample were screened for depression and then classified as depressed and non-depressed patients
	3	Ascertainment of exposure	Self-reported confirmed by reviewing secure record	*	Exposure identified by self-reported scale by participants during a face to face interview at the inclusion visit and further confirmed in clinical records
	4	Demonstration that outcome of interest was not present at start of study	Yes	*	Participants were excluded if they had a documented history of previous CVD
Comparability (2)	**1**	Study controls for age/sex	Yes	*	Age, sex, smoking, alcohol consumption, BMI, HTN, type 2 diabetes, dyslipidaemia and family history of premature CHD, and type Mediterranean diet intervention
	2	Study controls for at least 5 additional risk factors	Yes	*	
Outcome (3)	**1**	Assessment of outcome	Outcome ascertained by secure records	*	Cardiac outcomes were defined using medical records, data from GPs and death certificates
	2	Was follow-up long enough for outcomes to occur (≥10years)	No	0	The follow-up was for 7 years
	3	Adequacy of follow up of cohorts	Not reported	0	No statement about attrition rate
Total				**6**	

(Moise et al., 2016)					
Quality assessment criteria			**Authors' judgement**	**Score**	**Support for judgement**
Selection (4)	**1**	Representativeness of the exposed cohort	Cohort was representative of the average population	*	Cohort was a population-based study representative of black and white patients aged ≥45 years living in the US

	2	Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort	*	The same cohort sample were screened for depression and then classified as depressed and non-depressed patients
	3	Ascertainment of exposure	A self-reported depression scale	0	Exposure identified using 4-item-CES-D ≥4
	4	Demonstration that outcome of interest was not present at start of study	Yes	*	Patient were free of any CVD at baseline confirmed by interview, self-report or in-home examination
Comparability (2)	**1**	Study controls for age/sex	Yes	*	Age, sex, region, income, health insurance, education, and traditional CHD risk factors (systolic BP, total cholesterol, high-density lipoprotein cholesterol, and medication use [aspirin, statins, any antihypertensive medications], BMI, log of albumin: creatinine ratio, diabetes mellitus, pack-years of cigarette smoking, self-reported alcohol use, physical inactivity, medication adherence, log of high-sensitivity C-reactive protein, antidepressant use, QT interval corrected for heart rate, atrial fibrillation and left ventricular hypertrophy
	2	Study controls for at least 5 additional risk factors	Yes	*	
Outcome (3)	**1**	Assessment of outcome	Outcome ascertained by secure records	*	Endpoints ascertain by regular telephone contact with patients and retrieval of medical records
	2	Was follow-up long enough for outcomes to occur (≥10years)	No	0	The follow-up was for 9 years
	3	Adequacy of follow up of cohorts	Subjects lost to follow up unlikely to introduce bias	*	Lost to follow-up was < 20% (1.6%)
Total				**7**	

(Nabi et al., 2010a)					
Quality assessment criteria			**Authors' judgement**	**Score**	**Support for judgement**
Selection (4)	**1**	Representativeness of the exposed cohort	Cohort was representative of the average population	*	Cohort was a population-based study representative of the Finnish population
	2	Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort	*	The same cohort sample were screened for depression and then classified as depressed and non-depressed patients
	3	Ascertainment of exposure	A self-reported depression scale	0	Exposure identified using 21-item-BDI ≥10
	4	Demonstration that outcome of interest was not present at start of study	Yes	*	Patient were free of any CVD at baseline confirmed by hospital discharge register
Comparability (2)	**1**	Study controls for age/sex	Yes	*	Age, sex, education, alcohol consumption, sedentary lifestyle, smoking, obesity, hypertension or diabetes and incident CHD or incident CBVD
	2	Study controls for at least 5 additional risk factors	Yes	*	
Outcome (3)	**1**	Assessment of outcome	Outcome ascertained by record linkage	*	Endpoints ascertain by hospital discharge and mortality records
	2	Was follow-up long enough for outcomes to occur (≥10years)	No	0	The follow-up was for 7 years
	3	Adequacy of follow up of cohorts	Not reported	0	No statement about attrition rate
Total				**6**	

(Pequignot et al., 2013)					
Quality assessment criteria			**Authors' judgement**	**Score**	**Support for judgement**

Selection (4)	**1**	Representativeness of the exposed cohort	Cohort was representative of the average population	*	Cohort was a population-based study, sample was non-institutionalized, randomly selected from the electoral rolls of three large cities in Franc
	2	Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort	*	The same cohort sample were screened for depression and then classified as depressed and non-depressed patients
	3	Ascertainment of exposure	A self-reported scale	0	Exposure identified using 20-item CES-D ≥16
	4	Demonstration that outcome of interest was not present at start of study	Yes	*	Participants enrolled in the study only if they had no history of CHD or stroke based on face-to-face interviews using a standardised questionnaire
Comparability (2)	**1**	Study controls for age/sex	Yes	*	Age, sex, study centre, smoking status, alcohol consumption, high BP, impaired fasting glycaemia or diabetes, hypercholesterolemia, living alone, education level, Mini mental state examination
	2	Study controls for at least 5 additional risk factors	Yes	*	
Outcome (3)	**1**	Assessment of outcome	Outcome ascertained by secure records	*	Information on the cardiac event was obtained from medical records, interviews with the patient's physician and death certificates
	2	Was follow-up long enough for outcomes to occur (≥10years)	No	0	Follow-up was for a median of 5.3 years
	3	Adequacy of follow up of cohorts	Subjects lost to follow up unlikely to introduce bias	*	< 20% were lost to follow-up (3.05)
Total				**7**	

(Rahman et al., 2013)					
Quality assessment criteria			**Authors' judgement**	**Score**	**Support for judgement**
Selection (4)	**1**	Representativeness of the exposed cohort	Cohort was representative of the average population	*	The study participants were identified from the population-based Swedish Twin Registry
	2	Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort	*	The same cohort sample were screened for depression and then classified as depressed and non-depressed patients
	3	Ascertainment of exposure	secure record	*	Exposure identified linkage to the national patient register
	4	Demonstration that outcome of interest was not present at start of study	Yes	*	Participants with any CVD at baseline were excluded based on computer assisted telephone interview
Comparability (2)	**1**	Study controls for age/sex	Yes	*	Birth year, sex, smoking status, educational level, HTN, diabetes, alcohol intake and BMI
	2	Study controls for at least 5 additional risk factors	Yes	*	
Outcome (3)	**1**	Assessment of outcome	Outcome ascertained by secure records	*	Diagnosis of CVD outcome obtained through linkage to the national patient register
	2	Was follow-up long enough for outcomes to occur (≥10years)	No	0	The maximum follow-up time was 4 years
	3	Adequacy of follow up of cohorts	Not reported	0	No statement about attrition rate
Total				**7**	

(Rajan et al., 2020)					
Quality assessment criteria			**Authors' judgement**	**Score**	**Support for judgement**

Selection (4)	**1**	Representativeness of the exposed cohort	Cohort was truly representative of the average population	*	Cohort was a multicentre population-based study from 21 countries
	2	Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort	*	The same cohort sample were screened for depression and then classified as depressed and non-depressed patients
	3	Ascertainment of exposure	Diagnostic interview	*	Short form of the CIDI-SF; cut-off point 4 or more depressive symptoms
	4	Demonstration that outcome of interest was not present at start of study	Yes	*	Study enrolled CVD free participants
Comparability (2)	**1**	Study controls for age/sex	Yes	*	Age, sex, urban/rural residence, educational attainment, use of statins, disabilities former and current smoking and alcohol use, hypertension, diabetes, and social isolation index
	2	Study controls for at least 5 additional risk factors	Yes	*	
Outcome (3)	**1**	Assessment of outcome	Mixed of Self-reported Secure record and other source	0	Self-reported through standardised form, household interviews, medical records and death certificates
	2	Was follow-up long enough for outcomes to occur (≥10years)	Yes	*	Follow-up was for 14 years
	3	Adequacy of follow up of cohorts	Subjects lost to follow up unlikely to introduce bias	*	lost to follow-up was 2%
Total				**8**	

(Scherrer et al., 2011)					
Quality assessment criteria			**Authors' judgement**	**Score**	**Support for judgement**
Selection (4)	**1**	Representativeness of the exposed cohort	Cohort was selected group of users	0	Cohort participants data were obtained from inpatient and outpatient Veterans Administration electronic medical Records
	2	Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort	*	The same cohort sample were screened for depression and then classified as depressed and non-depressed patients
	3	Ascertainment of exposure	Record linkage (identified through ICD codes	*	Exposure identified using ICD-9 codes
	4	Demonstration that outcome of interest was not present at start of study	Yes	*	Cohort used medical records to identify participants free of any CVD at baseline
Comparability (2)	**1**	Study controls for age/sex	Yes	*	Age, sex, race, marital status, and insurance type
	2	Study controls for at least 5 additional risk factors	No	0	
Outcome (3)	**1**	Assessment of outcome	Outcome ascertained by secure records	*	Outcome was assessed by medical records and register database
	2	Was follow-up long enough for outcomes to occur (≥10years)	No	0	Follow-up time was for 7 years
	3	Adequacy of follow up of cohorts	Not reported	0	No statement about attrition rate
Total				**5**	

(Whang et al., 2009)					
Quality assessment criteria			**Authors' judgement**	**Score**	**Support for judgement**
Selection (4)	**1**	Representativeness of the exposed cohort	Cohort was selected group of users	0	Cohort enrolled only female nurses aged 30-55

	2	Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort	*	The same cohort sample were screened for depression and then classified as depressed and non-depressed patients
	3	Ascertainment of exposure	A self-reported scale	0	Exposure identified by administering 5-item-MHI <53,
	4	Demonstration that outcome of interest was not present at start of study	Yes	*	Participants completed a questionnaire about their medical history and those with CHD and stroke at baseline were excluded
Comparability (2)	**1**	Study controls for age/sex	Yes	*	Age, beginning year of follow-up, smoking status, BMI, alcohol intake, menopausal status and postmenopausal hormone use, usual aspirin use, multivitamin use, vitamin E supplement use, hypercholesterolemia, family history of MI, history of stroke, n-3-fatty acid intake (quintiles), alpha linoleic acid intake (quintiles), and moderate/vigorous physical activity, non-fatal CHD during follow-up, HTN and diabetes
	2	Study controls for at least 5 additional risk factors	Yes	*	
Outcome (3)	**1**	Assessment of outcome	Outcome ascertained by medical records and some events were further confirmed by physician who were blinded to the exposure	*	Outcome confirmed by medical records and death certificate, further confirmation included physician blinded to the exposure
	2	Was follow-up long enough for outcomes to occur (≥10years)	No	0	Follow-up time was 8 years
	3	Adequacy of follow up of cohorts	Not reported	0	No statement about attrition rate
Total				**5**	

(Wouts et al., 2008)					
Quality assessment criteria			**Authors' judgement**	**Score**	**Support for judgement**
Selection (4)	**1**	Representativeness of the exposed cohort	Cohort was selected group of users	*	Elderly population aged 55-85 years drawn from the population registers of 11 municipalities
	2	Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort	*	The same cohort sample were screened for depression and then classified as depressed and non-depressed patients
	3	Ascertainment of exposure	A self-reported scale	0	Exposure identified using 20-item CES-D ≥16
	4	Demonstration that outcome of interest was not present at start of study	Yes	*	Cardiac event confirmed either by self-reported, GP information or use of medication
Comparability (2)	**1**	Study controls for age/sex	Yes	*	Age, sex, Mini-Mental State Examination score, smoking, functional limitations, HTN, diabetes mellitus, and obesity
	2	Study controls for at least 5 additional risk factors	Yes	*	
Outcome (3)	**1**	Assessment of outcome	Outcome ascertained by record linkage	*	Cardiac event was ascertain by self-report confirmed by GP or a cardiac specialist confirming the GP diagnosis of stroke
	2	Was follow-up long enough for outcomes to occur (≥10years)	Yes	*	Follow-up time was for 10 years
	3	Adequacy of follow up of cohorts	Not reported	0	No statement about attrition rate
Total				**7**	

(White et al., 2015)					
Quality assessment criteria			**Authors' judgement**	**Score**	**Support for judgement**

Selection (4)	**1**	Representativeness of the exposed cohort	Cohort was selected group of users	0	Cohort enrolled HIV+ patients matched with HIV-
	2	Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort	*	The same cohort sample were screened for depression and then classified as depressed and non-depressed patients
	3	Ascertainment of exposure	Medical records	*	Exposure identified using electronic medical records diagnosed according to ICD-9
	4	Demonstration that outcome of interest was not present at start of study	Yes	*	participants at baseline were free of CVD defined using medical records
Comparability (2)	**1**	Study controls for age/sex	Yes	*	Age, sex, race/ethnicity, BMI, HTN, diabetes mellitus, LDL-c, HDL-c, triglycerides, statin use, hemoglobin, renal function, atrial fibrillation, atrial flutter, smoking status, alcohol abuse or dependence, cocaine abuse or dependence, and HCV infection
	2	Study controls for at least 5 additional risk factors	Yes	*	
Outcome (3)	**1**	Assessment of outcome	Outcome ascertained by secure records	*	Outcome determined by using medical health records and CVD diagnosed according to ICD-9
	2	Was follow-up long enough for outcomes to occur (≥10years)	No	0	Follow-up time was for 5.8 years
	3	Adequacy of follow up of cohorts	Not reported	0	No statement about attrition rate
Total				**6**	

(Wulsin et al., 2005)					
Quality assessment criteria			**Authors' judgement**	**Score**	**Support for judgement**
Selection (4)	**1**	Representativeness of the exposed cohort	Cohort was somewhat representative of the average population	*	Cohort randomly allocated sample of adult population ranged in age from 30 to 91 years
	2	Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort	*	The same cohort sample were screened for depression and then classified as depressed and non-depressed patients
	3	Ascertainment of exposure	A self-reported scale	0	Exposure identified using 20-item CES-D ≥16
	4	Demonstration that outcome of interest was not present at start of study	Yes	*	Baseline cardiac disease identified by examination of participant's medical history
Comparability (2)	**1**	Study controls for age/sex	Yes	*	Age, sex stratified, smoking, HTN, diabetes, BMI, total cholesterol, and alcohol consumption
	2	Study controls for at least 5 additional risk factors	Yes	*	
Outcome (3)	**1**	Assessment of outcome	Outcome ascertained by secure records and blind assessment	*	Events were reviewed using medical records and adjudicated by a panel of 3 physician investigators, blinded to the exposure
	2	Was follow-up long enough for outcomes to occur (≥10years)	No	0	Follow-up time was for 6 years
	3	Adequacy of follow up of cohorts	Lost to follow-up unlikely to introduce bias	*	< 20% were lost to follow-up
Total				**6**	

Appendix 3: Methodological quality of the cohort study (B

Assessment of the cohort study presented in chapter 7 by New-castle Ottawa scale tool					
Quality assessment criteria			**Authors' judgement**	**Score**	**Support for judgement**
Selection (4)	**1**	Representativeness of the exposed cohort	Cohort was selected group of users	*	The study focused on hypertensive particpants attending secondary and tertiary health care centre
	2	Selection of the non-exposed cohort	No control group (unexposed particpants)	0	There was no non-user group of antihypertensive drugs
	3	Ascertainment of exposure	Electronic records of prescription data	*	The present cohort relied on electronic records to extract data on prescription of antihypertensive drugs
	4	Demonstration that outcome of interest was not present at start of study	Yes	*	The present study relied on prescription data to ensure that participants were free of antidepressants prescriptions at least for 12 months before study entry. However, the measurement may not be an accurate tool as a proxy for clinical depression.
Comparability (2)	**1**	Study controls for age/sex	Yes	*	Age, sex, SBP, history of smoking, cholesterol, body weight, CCI and eGFR
	2	Study controls for at least 5 additional risk factors	Yes	*	
Outcome (3)	**1**	Assessment of outcome	Outcome ascertained by electronic records of prescription data	*	Outcome were determined using data from the (ISD). Again, antidepressants may not be a good proxy as a diagnostic criterion for depression
	2	Was follow-up long enough for outcomes to occur (≥ one year)	Yes	*	Follow-up period was for seven years
	3	Adequacy of follow up of cohorts	Complete follow up	*	100% completed the follow-up
Total				**7**	

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