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Depressive Symptoms Prior to and after Incident Cardiovascular Disease and Long-term Survival A population-based Study of Older Persons

Rosanne Freak-Poli[1,2*], Arfan Ikram M[1,3,4], Oscar H Franco[1], Albert Hofman[1,5] and Henning Tiemeier[1,6,7]

[1]Department of Epidemiology, Erasmus Medical Centre, Rotterdam, The Netherlands
[2]Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia
[3]Department of Neurology, Erasmus Medical Centre, Rotterdam, The Netherlands
[4]Department of Radiology, Erasmus Medical Centre, Rotterdam, The Netherlands
[5]Department of Epidemiology, Harvard University, MA 02138, USA
[6]Department of Child and Adolescent Psychiatry, Erasmus Medical Centre, The Netherlands
[7]Department of Psychiatry, Erasmus Medical Centre, The Netherlands

Abstract

Background: Depression after a CVD event is associated with increased mortality. However, little is known about how pre-existing depression affects survival after CVD incidence.

Aim: To evaluate whether depressive symptoms measured preceding first incident CVD (pre-CVD), as well as measured after CVD (post-CVD), affect survival.

Methods: From the Rotterdam Study, 6,932 persons aged 55+ and free of dementia and CVD completed the Center for Epidemiological Studies Depression (CES-D) scale every 4 to 5 years from 1993. CES-D subdomains were positive affect, negative affect, somatic symptoms and interpersonal affect. Persons were followed for mortality and CVD, defined as incident stroke, heart failure and coronary heart disease (CHD).

Results: During 15-year follow-up, 22% of participants suffered their first incident CVD. Depressive symptoms measured ≈3 years prior to first incident CVD were not associated with mortality after adjustment for smoking status and physical function (HR per 10-point score: 1.04, 95%CI: 0.97-1.10). Higher pre-CHD somatic symptoms were associated with greater CHD mortality and higher pre-stroke positive affect was associated with less stroke mortality. After first incident CVD, depressive symptoms increased. Higher depressive symptoms measured after CVD was associated with an increased risk for mortality (HR: 1.09, 95%CI: 1.00, 1.19). Higher post-CVD positive affect was protective of both all-cause and CVD mortality.

Conclusion: During 15-years follow-up in community-dwelling older adults, the relation between higher depressive symptoms measured before first incident CVD and mortality was not independent of health status. In contrast, higher depressive symptoms measured after CVD was associated with an increased risk for mortality.

Keywords: Depressive symptoms; Depression; Positive psychology; Well-being; Negative affect; Positive affect; Happiness; Cardiovascular disease; Stroke; Heart failure; Coronary heart disease; Aging; Prevention

Abbreviations: CVD: Cardiovascular Disease; HF: Heart Failure; CHD: Coronary Heart Disease; CES-D: Center For Epidemiological Studies Depression

Introduction

Epidemiological studies strongly suggest a bi-directional relation between depression and cardiovascular disease [1]. (CVD): depression is an independent risk factor for CVD [2-4] while depression occurs frequently after incident CVD [4,5]. Both depression and CVD independently affect an individual's survival. To inform preventive health strategies, it is important to attempt to disentangle the bi-directional relation between depression and CVD and understand the potential impact of pre-existing depression upon survival after a CVD event. Furthermore, there is a growing discussion regarding broadening mental health research to incorporate positive psychological well-being rather than the historical approach which has predominantly focused on the relation between poor psychological functioning with physical health and mortality [6,7].

A few studies have attempted to retrospectively assess pre-event depression in CVD patients when assessing the relation between depression and CVD survival [8] specifically asked patients to recollect their state of mind in the two weeks prior to presenting with the current episode of acute coronary syndrome. However, retrospective assessment is vulnerable to recall bias. Hence, it is preferable to measure pre-event depression prospectively. Prospective measurement requires a cohort that people with CVD are nested within. This cohort can either be followed over-time or later linked to outcome measurements, such as CVD incidence and mortality registration data [9] provide an example where registry data for coronary artery bypass grafting (CABG) operations and clinically diagnosed depression were linked, illustrating that history of depression was strongly associated with seven year mortality in patients who underwent primary isolated CABG on a non-emergency basis. However, the average age of [9] clinical sample was 67 years and depression could have been diagnosed at any time proceeding CABG operations.

In this paper we explore a novel approach by using an observational

***Corresponding author:** Rosanne Freak-Poli, Department of Epidemiology, Erasmus University Medical Centre, The Netherlands, Tel: +31 (0)107038490; E-mail: rosanne.freak-poli@monash.edu

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longitudinal study with repeated measures to obtain depression status prospectively assessed within a few years preceding a CVD event. Our main aim is to examine whether depressive symptoms assessed preceding first incident CVD (termed "pre") predicts mortality after first incident CVD. To compare with the main analysis and prior studies, we also examined whether depressive symptoms assessed after CVD (termed "post") predicts mortality. We also aim to assess whether one of the depressive symptoms subdomains of positive affect, negative affect, somatic symptoms or interpersonal affect is driving the relation between CVD and mortality.

Methods

Study population

The Rotterdam Study is a population-based cohort of older adults and has been approved by the Ministry of Health of the Netherlands [10]. This paper examines the 8,129 adults aged 55+ who undertook repeated examinations for depressive symptoms between 1993 and 2012, (Appendix 1). Measurements (except education and sport) were repeatedly measured up to four times, approximately five years apart. Participants were ineligible for the primary analysis if they had prevalent CVD (n=1,112), were demented (n=174), or did not provide data linkage permission (n=55) upon entry to the study. We followed 6,932 eligible participants for 15.4+2.8SD years. The main analysis constituted of 1,344 persons with incident CVD, who undertook depressive symptom examination preceding incident CVD and were cognitively able to complete a self-reported questionnaire (no dementia). For the analysis assessing post-CVD depressive symptoms as the predictor, participants who were originally excluded due to having prevalent CVD at entry to the study were combined with those who had depressive symptom measured after first incident CVD.

Depressive symptoms

The Center for Epidemiological Studies Depression [11] (CES-D) scale is a validated, widely used, standardised self-report instrument measuring current depressive symptoms and consists of 20 items, reported on a four-point scale indicating mood and feelings experienced in the past week from 0 to 3. The CES-D has four underlying subdomains: positive affect (four items), negative affect (seven items), somatic problems (seven items) and interpersonal relations (two items) [11,12]. We recalculated scores to a scale from 0 to 10 for interpretability (e.g. CES-D= [score*10]/ [20 questions*3 points]) and weighted if 25% or less of questions were missing (e.g. CES-D if 15 of 20 questions answered =[score*10]/[15 questions*3 points]*20/15). Scales were not standardized as this would assume a normal distribution, which the CES-D lacked even after attempts at transformation. As the CES-D was repeated, the measurement most proximally prior to the incidence of CVD was used. If dementia had been reported during or prior to the data collection time, a CES-D measurement prior to onset of dementia was utilized.

Incidence disease and mortality

CVD and its components of stroke, coronary heart disease (CHD) and heart failure (HF) were defined in accordance to standard procedure previously undertaken in the Rotterdam Study [13], which are based on the International Classification of Diseases, 10th revision (ICD-10) [14]. Incident and mortality data were obtained through continuously monitoring of day-to-day medical records and coded with agreement from two research physicians [13,15]. If incident CVD and mortality occurred on the same date, mortality was recoded to occur half a day later to ensure that the most severe cases of CVD were not excluded.

Confounders

Potential confounders were collected through self-report (demographics and lifestyle), independently (adiposity) or blood samples (biomedical). Potential confounders were tested to ensure they changed the association between depression symptoms with the outcome of interest by 10% [16,17], when included in the analysis assessing depressive symptoms as a predictor of mortality after first incident CVD, along with age, sex, education, marital status, smoking status and Activities of Daily Living [18,19]. Using this technique, the following were not considered confounders as they did not sufficiently modify the association of interest: living situation (independent, service flat, home for the elderly), alcohol status (never, past, current), sport status (yes/no), waist circumference (cm), weight (kg), height (cm), body mass index (kg/m^2), pulse (beats per minute), total cholesterol (mmol/L) and glucose (mmol/L).

Confounders were assessed in groups: Model 1: Demographics: Sex, education level (low, intermediate, high), marital status (partnered, unpartnered); Model 2: Model 1 + Health status: smoking status (never, past, current), waist to hip ratio (waist/hip circumference), CVD medication, systolic and diastolic blood pressure (mmHg), high density lipoprotein (HDL), diabetes status (yes/no) and Activities of Daily Living [18,19]. Analyses were additionally adjusted for cohort recruitment wave, CES-D data collection round, the time between CES-D collection and incident CVD, and ten-year birth cohort due to possible advances in medical management [20].

Statistical analyses

As the main analysis, the most recently available measurement of CES-D preceding first incident CVD (termed "pre") was assessed as a determinant of mortality after incident CVD in Cox regression. The measure of CES-D depressive symptoms, as well as its subdomains of negative affect, somatic symptoms, interpersonal affect or positive affect, was assessed as determinants. Mortality after incident composite CVD and after specific incident CVD outcome (stroke, HF, CHD) were assessed as outcomes. We then compared pre-CVD depressive symptoms by participation status, survival status, depression status and depression history status. We also compared pre-CVD and post incident CVD (termed "post") depressive symptoms for participants who completed data collection after their first incident CVD. Logistic and linear regressions were reported after adjusting for age, sex and education. To compare with the main analysis and prior studies, we also examined whether depressive symptoms assessed post-CVD as a determinant of increased mortality. This comparative analysis was undertaken in both (1) the participants who returned after their first CVD and (2) incorporating those with prevalent CVD at first data collection round.

We undertook a series of sensitivity analyses for the main analysis: First, we assessed whether the results of the main analysis depended on age (<75 years, >75 years) or sex. Secondly, the main analysis was repeated with CVD mortality as the outcome. Thirdly, reverse causality was assessed by exclusion of participants who died within six-months of depressive symptoms examination.

Regression models and summary statistics were run in Stata version 13 [21]. For Cox proportional hazards model, age was the origin (specifies when a subject first becomes at risk) and incident CVD date was entered (specifies when a subject first comes under observation, meaning that any failures, were they to occur, would be recorded in the data). Missing confounders were imputed (9% missing before exclusions) using the ice STATA command based on

Parameters	Scores[a]		Model 1[b] Demographic			Model 2[c] Health status		
	n	Events	Hazard Ratio	95% Confidence Interval	p value	Hazard Ratio	95% Confidence Interval	p value
Main Analysis								
Depressive Symptoms	1344	908	1.10	(1.05, 1.16)	<0.001	1.04	(0.97, 1.11)	0.1
Positive affect			0.96	(0.93, 0.98)	<0.001	0.98	(0.95, 1.00)	0.08
Negative affect			1.07	(1.01, 1.12)	0.01	1.03	(0.98, 1.08)	0.3
Somatic symptoms			1.07	(1.02, 1.12)	0.004	1.02	(0.97, 1.08)	0.5
Interpersonal affect			1.02	(0.95,1.09)	0.6	0.99	(0.93, 1.07)	0.9
By Cardiovascular Disease component[d]								
Stroke[e]								
Depressive Symptoms	504	368	1.11	(1.02, 1.21)	0.02	1.08	(0.98, 1.18)	0.1
Positive affect			0.93	(0.89, 0.97)	<0.001	0.93	(0.89, 0.98)	0.003
Negative affect			1.03	(0.95, 1.12)	0.5	1.02	(0.93, 1.10)	0.7
Somatic symptoms			1.06	(0.97, 1.15)	0.2	1.00	(0.91, 1.10)	1.0
Interpersonal affect			0.92	(0.78, 1.07)	0.3	0.87	(0.73, 1.02)	0.1
Heart Failure[f]								
Depressive Symptoms	440	362	1.14	(1.04, 1.24)	0.004	1.07	(0.97, 1.18)	0.2
Positive affect			0.94	(0.91, 0.98)	0.00	0.97	(0.93, 1.01)	0.2
Negative affect			1.14	(1.04, 1.24)	0.005	1.10	(1.01, 1.21)	0.04
Somatic symptoms			1.05	(0.98, 1.13)	0.2	1.00	(0.92, 1.08)	0.9
Interpersonal affect			1.16	(0.99, 1.37)	0.06	1.16	(0.98, 1.37)	0.08
Coronary Heart Disease[g]								
Depressive Symptoms	420	197	1.13	(1.01, 1.27)	0.04	1.07	(0.94, 1.22)	0.3
Positive affect			0.97	(0.92, 1.03)	0.4	1.01	(0.95, 1.07)	0.8
Negative affect			1.08	(0.97, 1.21)	0.2	1.04	(0.92, 1.17)	0.5
Somatic symptoms			1.19	(1.07, 1.32)	0.002	1.16	(1.03, 1.31)	0.02
Interpersonal affect			1.05	(0.93, 1.19)	0.4	1.07	(0.94, 1.22)	0.3

[a] Scores are units/10; scales are from zero to ten; each Hazard Ratio increase represents the response to a 10% increase in the score's effect.
[b] Age is the time-scale, stratified by birth cohort and adjusted for study cohort. Model 1 is adjusted for demographics: Sex, education level (low, intermediate, high), marital status (partnered, unpartnered).
[c] Model 2 is additionally adjusted for health status: smoking status (never, past, current), waist to hip ratio (waist circumference / hip circumference), CVD medication (current use of either cardiac therapy medication, anti-hypertensives, diuretics, beta blocking agents, calcium blockers, or ACE-inhibitors), systolic blood pressure (SBP; mmHg), diastolic blood pressure (DBP; mmHg), high density lipoprotein (HDL), diabetes status (yes/no) and Activities of Daily Living.
[d] Derived from a population of 6,932 at risk, followed for 15.4 ± 2.8SD years. CVD incidence censored at 1st April 2010, providing 7193 person-years of observation (mean 5.4 ± 4.4SD years; median 4.9; range: 0-19).
[e] Stroke incidence censored at 1st January 2012, providing 2,249 person-years of observation (mean 4.5 ± 4.3SD years; median 3.6; range: 0-18).
[f] HF incidence censored at 1st April 2010, providing 2,039 person-years of observation (mean 4.6 ± 3.9SD years; median 4.4; range: 0-16).
[g] CHD incidence censored at 1st January 2011, providing 2,898 person-years of observation (mean 6.9 ± 4.5SD years; median 6.6; range: 0-19).

Table 1: Pre-event depressive symptoms[a], and its subdomains, as predictors of mortality after first incident cardiovascular disease.

age, sex, education and prior repeated measures of the confounder of interest [22].

Results

When compared to the 5,588 participants without CVD during follow-up, the included participants with incident CVD were more likely to be older, male, unpartnered, in assisted living and generally less healthy at first measurement collection, (Appendix 2). Among the 1,344 included participants there were 874 (65.0%) deaths during the 6,884 person-years of observation (mean 5.1+4.3SD years; range:0-19). Repeated measures of pre-CVD depressive symptoms were generally moderately correlated (depressive symptoms r=0.46, positive affect r=0.25; negative affect r=0.48, somatic symptoms r=0.41, interpersonal affect r=0.23).

Pre-CVD CES-D depressive symptoms

Depressive symptoms measured prior to first incident CVD were associated with mortality after incident CVD when adjusting for demographics, (Table 1). However, after additionally adjusting for health status in Model 2 the relation between pre-CVD depressive symptoms and mortality reduced in magnitude and was no longer statistically significant. Through sensitivity analyses we determined that the main contributors to the null finding were the inclusion of smoking and physical function (data not reported). We observed no associations when the main analysis was stratified by age or sex, when reverse causality was assessed (HR: 1.04, p=0.2), or when CVD mortality was assessed as the outcome, Appendix 3. Findings did not alter when the time between depressive symptoms examination and incident CVD was restricted to one year (n=252, HR: 1.04, p=0.5) or six months (n=117, HR: 1.15, p=0.2).

Pre-CVD CES-D subdomains

When assessed in separate models, pre-CVD negative affect, somatic symptoms and positive affect (protective direction) shared the same pattern of association observed for depressive symptoms in the main analysis, (Table 1). Positive affect was positively associated with survival after stroke, negative affect was associated with mortality after heart failure and somatic symptoms with mortality after CHD. However, there was no statistically significant difference between associations of any of the four subdomains with a specific CVD outcome (overlapping confidence intervals, p>0.05), The relations between positive affect with mortality after stroke (HR: 0.94 per point, 95%CI: 0.89-0.99, p-value: 0.02) and somatic symptoms with mortality after CHD (HR: 1.28, 95%CI: 1.06-1.55, p-value: 0.01) held

Parameters	n	Depressive Symptoms			
		Pre-CVD		Post-CVD	
		Clinically depressed	Mean ± SD	Clinically depressed	Mean ± SD
I. Participation and Survival Status					
Participation Status post-CVD					
Returned	571	6%	0.80 ± 1.08	15%	1.35 ± 1.33
Did not return	773	13%	1.18 ± 1.31	-	-
Invited to return	762	13%	1.18 ± 1.31	-	-
Not invited to return	11	18%	1.37 ± 1.53	-	-
Survival Status, those who returned					
Non-fatal CVD and survived within follow-up time	340	5%	0.74 ± 1.00	11%	1.19 ± 1.25
Non-fatal CVD but died within follow-up time	231	8%	0.90 ± 1.18	20%	1.58 ± 1.40
Survival Status, those who did not return					
Fatal CVD event	42	17%	1.25 ± 1.37	-	-
Non-fatal CVD	731	12%	1.18 ± 1.31	-	-
Non-fatal CVD and survived within follow-up time	96	10%	0.94 ± 1.24	-	-
Non-fatal CVD but died within follow-up time	635	13%	1.22 ± 1.32	-	-
II. Participation and Depression Status					
Depressive status pre-CVD event, total sample					
Not depressed	1,209	0%	0.70 ± 0.72	-	-
Depressed	135	100%	3.90 ± 1.11	-	-
Depressive status pre-CVD event, those who returned					
Not depressed	534	0%	0.58 ± 0.65	12%	1.23 ± 1.23
Depressed	37	100%	3.96 ± 1.11	57%	3.00 ± 1.53
Depression status pre and post CVD event, those who returned					
Not depressed pre or post CVD event	470	0%	0.54 ± 0.61	0%	0.88 ± 0.75
Not depressed pre, but depressed post CVD event	64	0%	0.92 ± 0.81	100%	3.79 ± 1.07
Depressed pre, but not depressed post CVD event	16	100%	3.64 ± 0.94	0%	1.55 ± 0.65
Depressed pre and post CVD event	21	100%	4.20 ± 1.19	100%	4.10 ± 0.99
Depressive status pre-CVD event, those who did not return					
Not depressed	675	0%	0.79 ± 0.76	-	-
Depressed	98	100%	3.88 ± 1.11	-	-
III. Participation and Depression History					
Depressive status ever pre-CVD, total sample					
Never depressed	1,178	0%	0.69 ± 0.72	-	-
Depressed	166	100%	3.38 ± 1.52	-	-
Depressive status ever pre-CVD event, those who returned					
Never depressed	523	0%	0.57 ± 0.64	12%	1.22 ± 1.22
Depressed	48	81%	3.28 ± 1.64	50%	2.75 ± 1.62

Table 2: Exploration of depressive symptoms pre- and post- cardiovascular disease (CVD).

when subdomains were mutually adjusted, (Appendix 3). When CVD mortality was assessed as the outcome, pre-CVD positive affect was associated with CVD mortality survival.

Pre- versus post-CVD CES-D depressive symptoms

Participants who completed data collection after their first incident CVD (42%, n=571) had less depressive symptoms prior to incident CVD (mean difference: -0.27+0.07SE, p<0.001 after adjusting for age, sex and education) and were more likely to survive during follow-up (HR: 0.15, p<0.001) than those who did not return, (Table 2). Participants who died on the day of their first incident CVD were more depressed prior to incident CVD than returning participants (mean: 0.40+0.19SE, p=0.04), but no more depressed than other non-returning participants without post-CVD depression symptom score (mean: 0.13+0.21SE, p=0.5). After first incident CVD, depressive symptoms significantly increased (mean: 0.29+0.03SE, p<0.001), regardless of survival status during follow-up (mean depressive symptom difference between those who survived and died: 0.18+0.12SE, p=0.2). An additional 2% (n=31) of participants had clinically relevant depressive symptoms (CES-D>=16) in a prior data collection round, but was not depressed in the round directly before their first incident CVD. When a sensitivity analysis was undertaken using the highest pre-CVD depressive symptoms score for all participants (mean 1.21+1.28SD), the results did not change (HR: 1.04, p=0.1 fully adjusted model).

Post-CVD CES-D depressive symptoms

Participants who returned after their first CVD were combined with participants with prevalent CVD at first data collection round (n=870, of which 487 died during follow-up). Higher post-CVD depressive symptoms were associated with greater all-cause mortality; a 9% increase per point on a ten point scale in the fully adjusted model, (Table 3). Higher post-CVD positive affect was associated with both lower all-cause mortality and lower CVD mortality, Appendix 3. When analysis was restricted to participants who returned after incident CVD, the magnitude of the associations were stronger (Table 3).

Discussion

In this sample of community-dwelling, older adults, depressive

Parameters	n	Events	Model 1[b] Demographic			Model 2[c] Health status		
			Hazard Ratio	95% Confidence Interval	p value	Hazard Ratio	95% Confidence Interval	p value
Participants with prevalent CVD at study entry and returning participants with incident CVD during follow-up[d]								
Depressive Symptoms	870	487	1.14	(1.05, 1.23)	0.001	1.09	(1.00, 1.19)	0.04
Positive affect			0.92	(0.89, 0.95)	<0.001	0.93	(0.89, 0.97)	<0.001
Negative affect			1.01	(0.94, 1.09)	0.8	0.99	(0.91, 1.07)	0.8
Somatic symptoms			1.12	(1.04, 1.20)	0.002	1.06	(0.99, 1.15)	0.1
Interpersonal affect			0.91	(0.81,1.01)	0.08	0.90	(0.80, 1.01)	0.07
Returning participants: Post first incident CVD[e]								
Depressive Symptoms	571	231	1.16	(1.04, 1.29)	0.01	1.13	(1.00, 1.26)	0.046
Positive affect			0.95	(0.91, 0.99)	0.01	0.96	(0.91, 1.00)	0.05
Negative affect			1.00	(0.88, 1.15)	1.0	1.03	(0.89, 1.19)	0.7
Somatic symptoms			1.13	(1.02, 1.26)	0.02	1.10	(0.99, 1.24)	0.09
Interpersonal affect			1.03	(0.86,1.25)	0.7	1.07	(0.89, 1.30)	0.5

[a] Scores are units/10; scales are from zero to ten; each Hazard Ratio increase represents the response to a 10% increase in the score's effect.
[b] Age is the time-scale, stratified by birth cohort and adjusted for study cohort. Model 1 is adjusted for demographics: Sex, education level (low, intermediate, high), marital status (partnered, unpartnered).
[c] Model 2 is additionally adjusted for health status: smoking status (never, past, current), waist to hip ratio (waist circumference / hip circumference), CVD medication (current use of either cardiac therapy medication, anti-hypertensives, diuretics, betablocking agents, calcium blockers, or ACE-inhibitors), systolic blood pressure (SBP; mmHg), diastolic blood pressure (DBP; mmHg), high density lipoprotein (HDL), diabetes status (yes/no) and Activities of Daily Living.
[d] Participants who were originally excluded due to having prevalent CVD at entry to the study were combined with those who had a post-CVD depressive symptoms. Derived from a population of 6,932 at risk, followed for 15.4 ± 2.8SD years. CVD incidence censored at 1st April 2010, providing 6,627 person-years of observation (mean 7.6 ± 4.3SD years; median 7.4; range: 0-20).
[e] Derived from a population of 6,932 at risk, followed for 15.4 ± 2.8SD years. CVD incidence censored at 1st April 2010, providing 4,408 person-years of observation (mean 7.7 ± 3.2SD years; median 7.5; range: 0-16).

Table 3: Post cardiovascular disease depressive symptoms[a] and risk of mortality.

symptoms measured prior to first incident CVD predicted mortality after incident CVD, however, this association was not independent of health status. Higher pre-CHD somatic symptoms were associated with greater mortality post-CHD. Positive affect measured pre-CVD was protective of CVD mortality after first incidence of CVD and positive affect measured pre-stroke was protective of mortality after first incidence of stroke. Participants who completed data collection after their first incident CVD had less depressive symptoms prior to the event and were more likely to survive during follow-up than those who did not return. Higher post-CVD depressive symptoms clearly predicted mortality. Positive affect measured post-CVD was protective of both all-cause and CVD mortality.

There has been limited research assessing whether depression measured prior to incident CVD is associated with mortality. In a large prospective study of older adults, higher pre-event depressive symptoms were associated with a 21% increase of having a new incident or reoccurring episode of CVD, however the duration of follow-up was only one year [23]. A recent meta-analysis of retrospective studies reported that depression onset prior to incident CHD and recurrent depression predicted the composite outcome of cardiac morbidity or all-cause mortality [24]. However, for those not depressed at time of the CVD event, a retrospectively assessed history of depression was not independently associated with cardiac morbidity or all-cause mortality, which is in line with our findings. It is important to note that the results from the meta-analysis are not directly comparable to our results as they included studies that assessed pre-CVD depression retrospectively in patients and only one of the nine reviewed studies adjusted for physical ability. Similarly to our study, the one other study that has adjusted for self-rated physical ability also observed a large reduction in the association between depressive symptoms with CVD and mortality when physical ability was corrected for [25] postulated that self-reported physical disability is a proxy for the severity of pre-exisiting diseases, which are also determinants of CVD mortality. Although adjustment of physical ability seems mandatory in such an analysis, disability may also be part of the causal pathway from depression to CVD to mortality. We theories that ill-health, whether it be smoking status, lower physical function or pre-existing diseases, may mediate the effect of depression on CVD and mortality. Further research is needed using causal mediation and causal inference techniques to explore this relation.

The relation between higher post-CVD depression and increased mortality that we observed has previously been established in a number of cohorts [4,26-28]. As the majority of studies in this field are concerned with disease progression after a CVD event, they have restricted their samples to CVD patients. There are several methodological issues when assessing post-CVD depression. Firstly, by recruiting CVD patients the most severe cases are not captured, possibly be due to death or the healthy volunteer effect [29], giving rise to selection bias, reverse causality and residual confounding. Secondly, when assessing current depression after the CVD event, the results may be confounded by illness perception [30-32], psychological functioning such as coping [33], or CVD severity [34,35]. Alternatively, the hospital setting may make it difficult for patients to evaluate symptoms of depression such as loss of pleasure or interest and sleep or appetite disturbances [36]. Although we did not assess CVD severity, we theorize that the large number of participants who did not return were likely to have more severe CVD as they were more likely to die within the follow-up period than returning participants. Finally, chronic and new events of depression are commonly combined when assessed as the exposure, termed "depression after CVD event" [26,27] specifically limit their meta-analyses to depression occurring after an incidence of CVD and observe associations with increased mortality. However, there may be different associations with mortality depending upon whether depression was measured immediately after a CVD event or after hospital discharge [36,37]. By restricting analysis to post-CVD or retrospectively assessed measures, efforts to improve survival and disease progression have taken a narrow view. While we observed that depression preceding first incident CVD was not associated with survival, we did observe that depression increased significantly after incident CVD. Here we present an approach that allowed us to assess

the influence of health conditions on depressive symptom score prior to onset of chronic disease, which is particularly important for diseases with a bi-directional relation.

When we assessed whether CES-D subdomains were driving the associations, we observed two relations. Firstly, we observed that higher somatic symptoms measured preceding first incident CHD is specifically associated with greater mortality after CHD. Our finding is consistent with a review of 13 prospective studies reported that somatic symptoms were associated with CVD and mortality in CHD patients [38]. Secondly, we observed that positive affect measured after CVD was protective of both all-cause and CVD mortality, illustrating that potentially positive affect is underlying the relation between depressive symptoms and mortality. It has been proposed that the protective relation of positive psychological well-being upon CVD and mortality may function through various psychological [33], health behavioral [7,39-41] and biological mechanisms [7,42,43]. Most importantly, the mechanisms influencing ill-health via positive psychological well-being are theorized to be separate and independent to the mechanisms which influence ill-health through psychological ill-being (negative affect or depressive symptoms) [40,44]. Similarly to our study, five studies have observed that positive psychological well-being is generally protective of CVD mortality in healthy populations [7]. More recently, it has been suggested that positive affect moderates the relation between negative affect and mortality in HF and CHD rehabilitation patients [45]. The relations observed in our study between positive affect and somatic symptoms with mortality held when mutually adjusting for depressive symptom subdomains, including negative affect. Although the depressive symptoms subdomain relations were consistent in sensitivity analyses, caution is required when interpreting sub-analyses due to reduced power and multiple testing. Additionally, it is important to note that the overlapping confidence intervals clearly illustrate that the relations observed for positive affect and somatic symptoms were not significantly different from the relation between the other depressive symptom subdomains and mortality. Yet, given that positive affect measured after CVD was protective of mortality, our findings support the current theory that positive psychological well-being may independently influence physical health and should be incorporated within mental health research [6,7].

The main limitation of this paper is that the relation between depression, CVD and mortality could be mediated by cardiovascular treatment, treatment choices and CVD severity. Secondly, depressive symptoms were assessed as being experienced in the past week while the mean lag between symptom reporting and CVD incidence is 3.3+2.6SD years. However, findings did not change when this time frame was restricted to six months or one year. A limitation of the secondary analysis assessing post-CVD as a predictor of mortality is retainment bias as we observed that few participants returned after first incident CVD. Due to the healthy volunteer effect [29] and different sample recruitment strategies, caution is required when comparing the results of our study to clinical studies assessing post-CVD depression in patient populations. Finally, it is important to specify that mental health (whether it be depression or positive affect) may not directly impact CVD or mortality [46], but rather may contribute to micro-level changes such as worse or better health behavior, which over time contribute to mortality or survival.

The main strengths of this paper is the use of repeated prospective measures of depression assessed prior to incident CVD, in a large sample, followed for fifteen years with adjustment for a variety of confounders. Additional strengths include the validity of our outcome (medical records) and determinant variables (validated questionnaire).

Conclusion

This is the first paper to prospectively measure depressive symptoms prior to first CVD event within such a short time frame and it is one of the largest powered studies in the field of depression, CVD and mortality. Depressive symptoms measured prior to first incident CVD event predicted mortality after incident CVD; however, this association was not independent of health status in this sample of community-dwelling, older adults. In contrast, we observed that higher post-CVD depressive symptoms are associated with increased mortality. While we suggest that post-CVD analyses at large be evaluated with caution due to methodological issues, our findings suggest that post-event depressive symptoms, rather than pre-event, may be of greater importance for long-term survival after a CVD event and illustrates an opportunity for secondary prevention. We suggest that both self-report physical functioning and depressive symptoms are subjective measures that are not routinely assessed during a general practitioner visit and provide valuable information in determining risk of mortality before the onset of CVD. Given that positive affect was generally protective of mortality, our findings support the current theory that positive psychological well-being may independently influence physical health and should be explored in future research. Further assessment of these relations using similar methodology in other prospective cohorts is required to confirm these findings and better understand the mechanisms behind the association between depression and survival. Given the increasing availability of longitudinal data, this novel approach of evaluating a health condition prior to an incidence of chronic disease addresses various methodological challenges in prior research, including concerns about reverse causality and selective recall bias, and could be utilized in other fields of research.

Author Contributions

RFP takes responsibility for the integrity of the data, the accuracy of the data analysis and the statistical data analysis. RFP & HT undertook the analysis design and critical interpretation of the data. All authors contributed to the final version of the paper and have read, as well as, approved the final manuscript.

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