**Title:** Clinical and course characteristics of depression and all-cause mortality: A prospective population-based study.

**Authors:** Lasserre AM, Marti-Soler H, Strippoli MP, Vaucher J, Glaus J, Vandeleur CL, Castelao E, Marques-Vidal P, Waeber G, Vollenweider P, Preisig M

**Journal:** Journal of affective disorders

**Year:** 2016 Jan 1

**Issue:** 189

**Pages:** 17-24

**DOI:** 10.1016/j.jad.2015.09.010

# Clinical and course characteristics of depression and all-cause mortality: a prospective population-based study

Aurélie M Lasserre, MD*; Helena Marti-Soler, PhD†; Marie-Pierre F Strippoli, MSc*; Julien Vaucher, MD‡; Jennifer Glaus, PhD*; Caroline L Vandeleur, PhD*; Enrique Castelao, MSc*; Pedro Marques-Vidal, MD, PhD†; Gérard Waeber, MD‡; Peter Vollenweider, MD‡; Martin Preisig, MD, MPH*

*Center for Psychiatric Epidemiology and Psychopathology, Department of Psychiatry, Lausanne University Hospital, 1008 Prilly, Switzerland

†Institute of Social and Preventive Medicine (IUMSP), Lausanne University Hospital and University of Lausanne, 1011 Lausanne, Switzerland

‡Department of Internal Medicine, Lausanne University Hospital, 1011 Lausanne, Switzerland

Corresponding author: Aurélie M. Lasserre, Center for Psychiatric Epidemiology and Psychopathology, Department of Psychiatry, University of Lausanne, Site de Cery, 1008 Prilly, Switzerland, Phone : +41 21 314 22 95, Fax: +41 21 314 84 69, aurelie.lasserre@chuv.ch

## ABSTRACT

**Background:** Given the large heterogeneity of depressive disorders (DD), studying depression characteristics according to clinical manifestations and course is a more promising approach than studying depression as a whole. The purpose of this study was to determine the association between clinical and course characteristics of DD and incident all-cause mortality.

**Methods:** CoLaus|PsyCoLaus is a prospective cohort study (mean follow-up duration=5.2 years) including 35 to 66 year-old randomly selected residents of an urban area in Switzerland. A total of 3668 subjects (mean age 50.9 years, 53.0% women) underwent physical and psychiatric baseline evaluations and had a known vital status at follow-up (98.8% of the baseline sample). Clinical (diagnostic severity, atypical features) and course characteristics (recency, recurrence, duration, onset) of DD according to the DSM-5 were elicited using a semi-structured interview.

**Results:** Compared to participants who had never experienced DD, participants with current but not remitted DD were more than three times as likely to die (Hazard Ratio: 3.2, 95% CI: 1.1 – 10.0) after adjustment for socio-demographic and lifestyle characteristics, comorbid anxiety disorders, antidepressant use, and cardiovascular risk factors and diseases. There was no evidence for associations between other depression characteristics and all-cause mortality.

**Limitations:** The small proportion of deceased subjects impeded statistical analyses of cause-specific mortality.

**Conclusions:** A current but not remitted DD is a strong predictor of all-cause mortality, independently of cardiovascular or lifestyle factors, which suggests that the effect of depression on mortality diminishes after remission and further emphasizes the need to adequately treat current depressive episodes.

KEYWORDS: Depressive disorders, all-cause mortality, population-based study, remission, current depression, cardiovascular risk factors, lifestyle

## INTRODUCTION

The high mortality associated with mental disorders has been studied for several decades (Harris and Barraclough, 1998). An association between depression and mortality has also been observed in various studies (Cuijpers and Smit, 2002; Cuijpers et al., 2013, 2014; Harris and Barraclough, 1998; Schulz et al., 2002; Van den Akker et al., 2003; Wulsin et al., 1999). Indeed, a meta-analysis of community studies (Cuijpers and Smit, 2002) found a 1.8 times elevated mortality in depressed compared to non-depressed subjects. However, the results varied largely across studies, which was also reflected by a review of clinical and community studies (Wulsin et al., 1999) that documented 29 studies providing evidence for a positive association, 13 revealing no association and 15 providing a positive association only in subgroups.

The authors of previous reviews (Schulz et al., 2002; Wulsin et al., 1999) and meta-analyses (Cuijpers and Smit, 2002; Van den Akker et al., 2003) suggested that future research should measure covariates other than demographics, in particular lifestyle factors and physical comorbidity in order to better understand the possible mechanisms underlying the association between depression and mortality. Moreover, the review of Schulz et al. (Schulz et al., 2002) also showed that the type of instrument used to assess depression is an important source of variance across studies. Compared with negative studies, those that revealed a positive association between depression and mortality relied more frequently on a formal interview procedure than on depression rating scales. Indeed, depression rating scales are only rough indicators of clinical depression (Roberts and Vernon, 1983), hardly allow characterization into depression subtypes and do not take into account the frequent occurrence of comorbid mental disorders or past psychopathology. Given the large heterogeneity of depression in terms of symptom manifestations, course and response to pharmacological treatment (Antonijevic, 2006; Ghaemi and Vohringer, 2011), studying characteristics of depression according to clinical

manifestations and course is likely to be a more promising approach than studying depression as a whole and could also help to better understand the partially inconsistent results of previous research regarding the association between depression and all-cause mortality. However, up to this date the association between course characteristics, such as the age of onset (Ferentinos et al., 2015) or the time spent in episodes has hardly been studied, whereas a recent community study showed the recency of depression to be associated with mortality due to ischemic heart disease mortality (Surtees et al., 2008). Moreover, although the results of recent studies suggest that among the depression subtypes the atypical one was most strongly associated with cardiovascular risk factors (Glaus et al., 2013; Lamers et al., 2013; Lasserre et al., 2014), the association between this subtype and mortality has not yet been examined.

The present prospective population-based cohort study designed to determine the association between depressive disorders (DD) and incident all-cause mortality over a 5-year follow-up period attempted to overcome a series of limitations of previous research by 1) the use of a semi-structured diagnostic interview that also assessed clinical (diagnostic severity level, atypical features) and course characteristics (recency, recurrence, time spent in episodes, age of onset) of (DD) and 2) the assessment of a large array of other risk factors including socio-demographic and lifestyle (smoking, alcohol use and inactivity) characteristics, comorbid anxiety disorders, antidepressant use as well as preexistent cardiovascular diseases and cardio-metabolic risk factors (obesity, hypertension, dyslipidemia and diabetes mellitus). Accordingly, the established association between DD and all-cause mortality with adjustment restricted to demographic characteristics only of the present study should be comparable with findings of previous research that also relied on formal depression diagnoses. However, in contrast to previous research the present study also allowed us to test whether this association was independent of a series of other risk factors such as lifestyle characteristics, antidepressant use

and physical conditions. Similarly, we could determine the influence of clinical and course characteristics of DD on the risk of dying.

## METHODS

### *Study design and participants*

The present paper used data from CoLaus|PsyCoLaus, a prospective cohort study designed to assess the associations between mental disorders and cardiovascular diseases (CVD) or cardiovascular risk factors in the community. The sample was randomly selected from the residents of the city of Lausanne (Switzerland) in 2003 according to the civil register (Firmann et al., 2008). Sixty-seven percent of the 35 to 66 year-old subjects who underwent the physical exam (CoLaus; n=5535) between 2003 and 2006 also accepted the psychiatric evaluation (PsyCoLaus) (Preisig et al., 2009), which resulted in a sample of 3720 individuals who had both the somatic and psychiatric evaluation. The sex distribution of the PsyCoLaus sample did not differ significantly from that of the general population in the same age range (Preisig et al., 2009). Although the youngest 5-year band of the cohort was underrepresented and the oldest 5-year band overrepresented, participants of PsyCoLaus and individuals who refused to participate revealed comparable scores on the General Health Questionnaire (GHQ-12 (Goldberg, 1972), French translation (Bettschart and Bolognini, 1996)), completed during the somatic exam. Six subjects needed to be excluded from the present analyses because of incomplete information on depressive episodes.

All subjects who participated at baseline were invited to a first follow-up evaluation between April 1$^{st}$, 2009 and July 31, 2012, which allowed us to assess the vital status of 3668 out of the 3714 subjects (98.8%) who had valid information on depressive episodes at the psychiatric baseline evaluation. The reminders (46 subjects) had all moved away from Switzerland. These

subjects were more likely to be physically inactive (62.2% vs. 44.2%) and to have a history of CVD (8.7% vs. 2.5%). The median follow-up period of the cohort was 5.2 years (s.d.: 0.8 years) corresponding to 19143 person-years.

*Assessments*

Diagnostic information on mental disorders was collected using the semi-structured Diagnostic Interview for Genetic Studies (DIGS), which was developed and extensively validated by the NIMH Molecular Genetics Initiative (Nurnberger et al., 1994). The French translation (Leboyer et al., 1995) also revealed excellent inter-rater reliability for major DSM-IV disorders (Berney et al., 2002; Preisig et al., 1999) and minor depression (Vandeleur et al., 2014), whereas the 6-week test-retest reliability was slightly lower (Berney et al., 2002; Preisig et al., 1999). The DIGS was completed with anxiety disorder sections of the Schedule for Affective Disorders and Schizophrenia - Lifetime Version (SADS-L) (Endicott and Spitzer, 1978). Major Depressive Disorders (MDD) and Other Specified Depressive Disorders (OSDD) including short-duration depressive episodes (4-13 days) and depressive episodes with insufficient symptoms (depressed affect and at least one of the other eight symptoms of a major depressive episode) were diagnosed according to the DSM-5. According to the suggestions of Angst and colleagues (Angst et al., 2002) a depressive disorder was considered as atypical if one or more episodes met at least 3 out of the 5 criteria of the DSM specifier for atypical features (the specifier is identical for DSM-IV and DSM-5): 1) mood reactivity, 2) significant weight gain or increase in appetite, 3) hypersomnia, 4) leaden paralysis and 5) interpersonal rejection sensitivity). Given the ongoing controversy regarding the definition of atypical features (Parker et al., 2002; Thase, 2009), we have chosen the none-hierarchical approach recommended by Angst and colleagues (Angst et al., 2002), which in contrast to DSM-IV and DSM-5, does not require the presence of mood-reactivity. A DD was considered as current if the criteria for a depressive episode were

met at the time of the baseline interview and remitted if the lifetime criteria for DD were fulfilled but the criteria for a current depressive episode were not met at the baseline assessment. The time spent in episodes was assessed by adding up the duration of all depressive episodes that the participants had reported. Age of onset was the age of onset of the first recalled episode of the DD. The two latter variables were dichotomized at the median (one year and 33 years, respectively). A lifetime anxiety disorder was diagnosed if the participant fulfilled the criteria for generalized anxiety disorder, social phobia, panic disorder or agoraphobia. Interviewers were required to be master-level psychologists, who were trained over a two month-period. They received ongoing supervision throughout the study by an experienced senior psychologist.

Information on socio-demographic and lifestyle (current smoking, number of alcoholic drinks a week, physical activity) characteristics as well as medical history and current medication was elicited using structured interviews. Socio-economic status (SES) was determined according to the Hollingshead scale (Hollingshead, 1975). The physical evaluation included the measurements of body weight, height and blood pressure as well as the collection of venous blood samples. Subjects were considered as physically inactive if they did not report leisure time physical exercise for at least 20 minutes twice a week. A self-reported history of CVD included coronary heart diseases (myocardial infarction, angina pectoris, pacing and coronary revascularization), stroke or peripheral arterial disease. Dyslipidemia was defined as HDL-cholesterol <1 mmol/l or LDL-cholesterol ≥4.1 mmol/l or triglycerides ≥2.2 mmol/l or lipid-lowering treatment. Obesity was defined as a Body Mass Index (BMI) ≥30 kg/m$^2$. Hypertension was defined as a systolic blood pressure ≥140 mm Hg or a diastolic blood pressure ≤90 mm Hg or anti-hypertensive treatment. Diabetes was defined as fasting blood glucose ≥7 mmol/l or diabetes treatment.

The vital status of the participants was systematically ascertained at the first follow-up exam. All participants of the baseline investigation received letters explaining them the follow-up exam. In a second step they were contacted by phone in order to schedule the follow-up exam. If the letter was returned by the post office because the subject had moved away or if subjects could not be reached by phone, the civil register of the community in which the subjects was living at the time of the baseline exam was systematically perused to obtain information on address changes or the occurrence and date of death. In case of a move within Switzerland, the civil register could always provide us with the names of the communities subjects had moved to. If they could not be reached at their new address, we verified their vital status through the civil register of their new community. However, if subjects had moved outside of Switzerland the civil register could not provide us with information on the subjects' new address. This was the unique reason for missing information on the subjects' vital status (n=46).

If a relative or the civil register had informed us that a subject had died we established the cause of death using all available sources of information: 1) general practitioners; 2) any hospital in Switzerland where the death had occurred; 3) the pre-hospital emergency care unit of the City of Lausanne; 4) the forensic medicine department of the University Hospital of Lausanne; 5) the *Swiss Statistics of the Swiss Confederation* (governmental agency providing death statistics based on official death certificates). If medical records were available the causes of death was adjudicated by 2 internal medicine specialists. Owing to the lack of accuracy of official death certificates, (Ives et al., 2009), the latter were only used to assign the cause of death in the absence of medical records.

*Statistical analysis*

All analyses were performed using the Statistical Analysis System version 9.3 for Windows (SAS Institute, Inc., Cary, NC, USA). Univariate analyses were conducted using chi-square or Student's t-tests as appropriate. The association between DD or characteristics of DD and mortality was assessed using serially adjusted proportional hazard models. The association between the following depression characteristics and mortality were assessed: diagnostic severity level (MDD vs. OSDD vs. none), clinical subtype (atypical vs. non atypical depression vs. none), recency (current vs. remitted vs. none), recurrence (recurrent vs. single episode vs. none), time spent in episode (at least one year [median] vs. less than one year vs. none) and age of onset (before 33 years [median] vs. 33 years or later vs. none). These associations were first established in separate models for each characteristic (Model 1) with adjustment for demographic characteristics (age, sex, SES, living alone and ethnicity), anxiety disorders (generalized anxiety disorder, social phobia, panic disorder, agoraphobia), lifestyle factors (inactivity, smoking, alcohol consumption), cardio-metabolic conditions (obesity, hypertension, dyslipidemia, diabetes), a history of CVD and current antidepressant use. In a next step, the six characteristics of DD were allowed to compete in the same model. This model was first adjusted for socio-demographic characteristics (Model 2) and then also for anxiety disorders, lifestyle factors, cardio-metabolic conditions, a history of CVD and current antidepressant use (Model 3). The proportional hazards assumption was verified for all the characteristics of depression. Missing data (25 for physical activity, 10 for anxiety disorder status) were compensated with multiple imputations (Makov Chain Monte Carlo method (Schafer, 1997; White et al., 2011) and Rubin's multiple imputation strategy (Rubin, 1987; Sterne et al., 2009)).

*Ethics approval*

The Institutional Ethics' Committee of the University of Lausanne approved the CoLaus

(approvals 16/03 and 33/09) and subsequently the PsyCoLaus study (approvals 134/05 and 239/09). All participants signed a written informed consent after having received a detailed description of the goal and funding of the study.

## RESULTS

### *Baseline characteristics of the sample*

Subjects with a lifetime DD were more likely to be women and to be younger, to live alone, to have a lifetime history of anxiety disorders (generalized anxiety disorder, social phobia, panic disorder or agoraphobia), to be smokers, to drink less alcohol, to have less hypertension and dyslipidemia and to use more antidepressants than never depressed subjects (Table 1). About 80% of subjects with a DD met criteria for MDD and about a sixth fulfilled criteria for atypical features or exhibited a current depressive episode at the time of the psychiatric interview, more than a third of subjects with a DD experienced recurrent episodes and nearly half of them reported episodes lasting a year or more, or an onset before 33 years.

### *All-cause mortality associated with DD*

During the follow-up, 56 subjects (1.6%; 2.3% of men, 1.0% of women) had died. Subjects with and without a lifetime history of a DD (1.3% vs. 1.8%, respectively; hazard ratio [HR] = 0.90; 95% Confidence Intervals [C.I.] 0.52-1.57) did not differ after adjustment for socio-demographic variables, comorbid anxiety disorders, current antidepressant use as well as cardiovascular risk factors and diseases.

### *All-cause mortality associated with depression characteristics*

The crude and adjusted associations between specific characteristics of DD and all-cause mortality in the whole sample are provided in Table 2. The table also shows the associations between potential confounders and all-cause mortality according to proportional hazard models. According to the crude associations in terms of unadjusted HRs subjects with remitted or recurrent DD and subjects with DD that started before the age of 33 years were at a lower risk of dying during the follow-up period. In a second step (Model 1) we run proportional hazard models separately for each of the 6 characteristics of DD with adjustment for demographic characteristics, anxiety disorders, lifestyle variables, cardio-metabolic diseases, a history of CVD and current antidepressant use (results not shown). Regardless of the number of variables models were adjusted for only current DD was significantly associated with mortality (HR for current DD according to the fully adjusted model = 2.32, 95%CI 1.12-4.80), whereas the other characteristics of DD that were negatively associated with the risk of dying according to the crude HRs were not associated with mortality any longer (remitted DD: HR 0.62, 95%CI 0.33-1.19; recurrent DD: HR 0.42, 95%CI 0.14-1.24; age of onset before 33 years: HR 0.61, 95%CI 0.26-1.43). The fact that the unadjusted association between current DD and all-cause mortality did not meet significance criteria was due to confounding by sex and age; i.e. participants with a current DD were more likely to be women and younger, which were both negatively associated with mortality. In the next step all depression characteristics were simultaneously introduced in the same proportional hazard model adjusted for socio-demographic characteristics (Model 2) and subsequently also for anxiety disorders, lifestyle variables, cardio-metabolic diseases, a history of CVD current antidepressant use (Model 3). In order to avoid overspecification of the model, we could only enter the two levels of the depression characteristic recency (current vs. remitted), whereas for the other characteristics of DD the intermediate level needed to be dropped. According to these models, participants with current DD at baseline revealed significantly and more than three times elevated mortality (Table 2). Among the covariates a history of CVD was most strongly associated with mortality, followed by current smoking, living

alone, male sex, inactivity and increasing age. Interestingly, the HR for a history of CVD was close to that of a current DD (3.50 vs. 3.23) and each of the two HRs lay within the 95% C.I. of the other HR.

As the HRs for subjects exhibiting a current depressive episode and that for subjects in remission at baseline differed significantly (the HR for subjects with current DD lay above the upper bound of the 95% C.I. of the HR for subjects with remitted DD and the HR for subjects with remitted DD lay below the lower bound of the 95% C.I. of the HR for subjects with current DD) regardless of the number of adjustments, we compared the two groups of subjects with DD regarding other characteristics (Table 3). These two groups did not differ in socio-demographic characteristics except for socio-economic status. However, the subjects with current DD were more likely to have a lifetime history of anxiety disorders, to be obese or inactive, to have antidepressant treatment, to meet criteria for a MDD rather than an OSDD, to exhibit an atypical depression subtype, to have a recurrent DD and to have spent more than one year in depression. Although these differences suggest higher severity of current depression, the HRs for current and remitted depression still significantly differed after an additional adjustment for lifetime social functioning (GAF score) as a supplementary indicator of disorder severity (HR = 3.16, 95% 1.02-9.82 and HR = 0.98, 95% 0.38-2.54, respectively). Regardless of the number of adjustments the HR for remitted depression always lay below the lower bound of the 95% C.I. of the HR for current depression.

*Cause-specific mortality by depression status*

Table 4, provides the results of the analyses regarding the associations between current/remitted depression status and specific causes of death. The HRs derived from

proportional hazard models were adjusted for the other assessed depression characteristics, demographic and lifestyle variables, anxiety disorders, cardio-metabolic diseases and antidepressant use. Due to the small number of events, only the strong association between current DD and cardio-vascular death reached the level of statistical significance. However, given that the established HRs for the other causes of death lay all within the wide 95% C.I. of the HR for cardiovascular death, our results do not suggest that excess mortality related to current depression was attributable to one specific cause of death.

## DISCUSSION

The present study is, to our knowledge, the first to prospectively assess all-cause mortality associated with clinical and course-related features of depressive disorders in the community with adjustment for a comprehensive array of potential confounding covariates including socio-demographic and lifestyle characteristics, comorbid anxiety disorders, antidepressant use, a history of CVD as well as accurately measured cardiovascular risk factors. The most salient finding was that subjects with a current but not a remitted depressive disorder were more than three times as likely to die within a 5-year follow-up period than never depressed subjects. The magnitude of the risk of currently depressed subjects to die was nearly as high as that of subjects with a history of a CVD. Among all the clinical or course-related characteristics of depression, it was only the recency of depression that was associated with all-cause mortality.

Our results presented need to be viewed in the light of several limitations. First, the proportion of subjects who died was relatively small which impeded accurate analyses of cause-specific mortality. Second, for 46 subjects (1.2%) we could not determine the vital status at follow-up because all of them moved away from Switzerland. Considering the small proportion of subjects

with missing vital status and given that there is hardly a reason to assume that the association between DD and mortality differs between subjects who moved away from Switzerland and those who stayed in the country, it is unlikely that the loss of subjects due to missing vital status at follow-up had introduced a sizable bias. Third, we did not collect information on dietary patterns, help-seeking behaviors or non-adherence to treatment although these variables could have contributed to the association between depression and mortality (Cuijpers and Schoevers, 2004; Mykletun et al., 2007; Wulsin et al., 1999) and we did not assess other physical conditions than cardio-metabolic conditions. Fourth, our study was conducted in an urban area of Switzerland. However, although the particular features of the sample are likely to affect the prevalence estimate of depression, it is less likely that they significantly influenced the prospective association between depression characteristics and mortality. Fifth, the lifetime prevalence of DD is rather high compared to other population-based studies (Kessler et al., 2003). However, given that semi-structured diagnostic interviews conducted by trained interviewers entail higher prevalence estimates of depression than fully structured interviews conducted by lay interviewers according to previous research comparing the two types of diagnostic instruments, our high lifetime prevalence of DD is likely to be attributable to the use of a semi-structured interview (Eaton et al., 2000). Moreover, although the use of a potentially more valid semi-structured rather than a fully structured diagnostic interview was likely to affect the prevalence estimate of DD, it is less likely that it significantly affected the assessed prospective associations between DD subtypes and mortality.

Our finding of excess mortality in subjects with current depression is consistent with those of previous research (Cuijpers and Smit, 2002; Schulz et al., 2002; Van den Akker et al., 2003; Wulsin et al., 1999), as the bulk of these studies were generally restricted to current or recent depressive episodes. However, compared to previous research in the community, which

generally relied on depression rating scales, the observed magnitude of the association between depression and mortality was higher. This is consistent with the review of Schulz et al (Schulz et al., 2002), which showed that studies relying on diagnostic interviews more frequently found a positive association between depression and mortality.

Interestingly, in our study, subjects with remitted depressive episodes at the moment of the baseline evaluation revealed a significantly lower mortality than subjects with current depression. Their unadjusted risk to die was even significantly lower than that for never depressed subjects, although their hazard ratio failed to reach the level of statistical significance after multiple adjustments. Although compared to those who were in a current depressive episode at baseline the remitted depressives were more likely to experience a less severe DD according to several indicators of severity (SES, comorbid anxiety disorder, inactivity, antidepressant treatment, fulfillment of criteria for MDD, recurrency and time spent in most severe depressive episode), depression severity could hardly explain the differential mortality rates between the current and remitted depression groups given that our analyses adjusted for all these severity indicators. Similar findings of associations between mortality and current or recent but not remitted depressive episodes have been observed in two previous community studies, the ECA (Bruce et al., 1994), and the EPIC Norfolk study (Surtees et al., 2008). Moreover, in the latter study, mortality was significantly lower for episodes that remitted more than 12 months prior to the assessment than for current depressive episodes and was even slightly lower than that observed in never depressed subjects, although the latter association did not reach the level of statistical significance. Several hypotheses could explain the distinct effects of current and remitted depression on mortality: 1) measurement errors are more pronounced for remitted than for current depressive episodes (Surtees et al., 2008), 2) subclinical manifestations of a physical disease predispose to both current depression and the

full blown disease that ultimately causes death (Surtees et al., 2008), 3) subjects exhibiting current depression are affected by a more severe disorder than those with remitted depression, and 4) the effect of depression on mortality decreases after remission. The first hypothesis appears unlikely given that measurement errors alone could hardly have attenuated the established hazard ratio for the association between remitted depression and mortality to less than 1 as observed in the present study, which was based on a semi-structured diagnostic interview. Indeed, the test-retest reliability for MDD assessed through such interviews has shown to be acceptably high even for intervals of up to 5 years (Prusoff et al., 1988). Regarding the second hypothesis, given that previous research has shown depression to be a risk factor for all major disease-related causes of death (Mykletun et al., 2007) it is unlikely that subclinical manifestations of these different diseases systematically preceded the depressive episodes observed at the time of the interview. The third hypothesis is hardly compatible with our findings given that the associations between the two types of depression and mortality did not change after adjustment for all typical severity characteristics. Our results rather support the fourth hypothesis, which is also compatible with a meta-analysis that documented a lower relative risk of dying in studies with longer follow-up periods (Van den Akker et al., 2003), but not others (Cuijpers and Smit, 2002; Wulsin et al., 1999). The observed excess mortality in currently depressed subjects in conjunction with a possibly diminished risk of dying in remitted subjects in our and similarly in the EPIC-Norfolk cohort study (Surtees et al., 2008) could indicate an increased vulnerability of currently depressed subjects and potential resilience of those who survived the acute episode.

Although we were not able to accurately determine disease-specific mortality rates in subjects with current depression because of a limited number of subjects who died during follow-up, our data do not suggest that the elevated mortality is attributable to one specific cause of death.

This corroborates previous findings (Angst et al., 2012; Mykletun et al., 2007) and a meta-analysis that demonstrated comparable depression-related excess mortality in cancer, heart and kidney disease patients, suggesting the implication of generic rather than disorder-specific mechanisms (Cuijpers et al., 2014). Interestingly, in contrast to a Canadian community study, which however assessed 12-month rather than current major depressive episodes (MDE) (Patten et al., 2011), our data support current depression as an independent predictor of all-cause mortality as the magnitude of the association remained unchanged after multiple adjustments.

Among the clinical manifestations and course features of depression, only the recency of episodes was predictive for mortality, which extends previous findings restricted to ischemic heart disease mortality (Surtees et al., 2008). It is remarkable that mortality did not differ between depressive subjects above and below the diagnostic threshold of MDD, which is consistent with a recent meta-analysis (Cuijpers et al., 2013), and further supports the clinical relevance of the newly defined DSM-5 category of OSDD. Regarding the atypical depression subtype, which has previously been found to be associated with metabolic diseases (Glaus et al., 2013; Lamers et al., 2013; Lasserre et al., 2014), our data did not provide evidence for higher mortality in subjects exhibiting this depression subtype.

Regarding the assessed covariates, it was not surprising that a history of CVD, current smoking and lack of activity were associated with mortality. It was more remarkable but consistent with some previous evidence (Udell et al., 2012) that we also observed a significant association between living alone and mortality. In contrast and similar to the HUNT study (Mykletun et al., 2007) we did not find anxiety disorders to predict mortality. Moreover, antidepressant use was

not associated with mortality, which contrasts with findings of Ryan et al (Ryan et al., 2008), who reported an association between antidepressant use and mortality in men.

In conclusion, the present results support a significant association between current but not remitted depressive episodes and all-cause mortality. This association was similar in size to that of a history of CVD. Accordingly clinicians should consider current depression as a life-threatening condition. The fact that only current depression was associated with mortality underscores the need to take the time-point of the occurrence of depressive episodes into account in future studies and suggests that the effect of depression on mortality diminishes after remission. Future studies should carefully examine clinical depression, potential confounding or mediating variables and causes of death in order to gain additional insight into the mechanisms underlying the complex association between depression and mortality. These studies should include a more comprehensive range of both somatic conditions and behavioral factors and follow the participants over a longer period of time than the previous studies.

## REFERENCES


Angst, J., Gamma, A., Sellaro, R., Zhang, H., Merikangas, K., 2002. Toward validation of atypical depression in the community: results of the Zurich cohort study. Journal of affective disorders 72, 125-138.

Angst, J., Hengartner, M.P., Gamma, A., von Zerssen, D., Angst, F., 2012. Mortality of 403 patients with mood disorders 48 to 52 years after their psychiatric hospitalisation. European archives of psychiatry and clinical neuroscience.

Antonijevic, I.A., 2006. Depressive disorders -- is it time to endorse different pathophysiologies? Psychoneuroendocrinology 31, 1-15.

Berney, A., Preisig, M., Matthey, M.L., Ferrero, F., Fenton, B.T., 2002. Diagnostic interview for genetic studies (DIGS): inter-rater and test-retest reliability of alcohol and drug diagnoses. Drug & Alcohol Dependence 65, 149-158.

Bettschart, W., Bolognini, M., 1996. Questionnaire de santé, GHQ-12, In: Guelfi, J.D. (Ed.), L'évaluation clinique standardisée en psychiatrie. Tome I. Editions Médicales Pierre Fabre, Boulogne, p. 157.

Bruce, M.L., Leaf, P.J., Rozal, G.P., Florio, L., Hoff, R.A., 1994. Psychiatric status and 9-year mortality data in the New Haven Epidemiologic Catchment Area Study. The American journal of psychiatry 151, 716-721.

Cuijpers, P., Schoevers, R.A., 2004. Increased mortality in depressive disorders: a review. Current psychiatry reports 6, 430-437.

Cuijpers, P., Smit, F., 2002. Excess mortality in depression: a meta-analysis of community studies. Journal of affective disorders 72, 227-236.

Cuijpers, P., Vogelzangs, N., Twisk, J., Kleiboer, A., Li, J., Penninx, B.W., 2013. Differential mortality rates in major and subthreshold depression: meta-analysis of studies that measured both. The British journal of psychiatry : the journal of mental science 202, 22-27.

Cuijpers, P., Vogelzangs, N., Twisk, J., Kleiboer, A., Li, J., Penninx, B.W., 2014. Comprehensive meta-analysis of excess mortality in depression in the general community versus patients with specific illnesses. The American journal of psychiatry 171, 453-462.

Eaton, W.W., Neufeld, K., Chen, L.S., Cai, G., 2000. A comparison of self-report and clinical diagnostic interviews for depression: diagnostic interview schedule and schedules for clinical assessment in neuropsychiatry in the Baltimore epidemiologic catchment area follow-up. Arch Gen Psychiatry 57, 217-222.

Endicott, J., Spitzer, R.L., 1978. A diagnostic interview: the schedule for affective disorders and schizophrenia. Archives of general psychiatry 35, 837-844.

Ferentinos, P., Koukounari, A., Power, R., Rivera, M., Uher, R., Craddock, N., Owen, M.J., Korszun, A., Jones, L., Jones, I., Gill, M., Rice, J.P., Ising, M., Maier, W., Mors, O., Rietschel, M., Preisig, M., Binder, E.B., Aitchison, K.J., Mendlewicz, J., Souery, D., Hauser, J., Henigsberg, N., Breen, G., Craig, I.W., Farmer, A.E., Muller-Myhsok, B., McGuffin, P., Lewis, C.M., 2015. Familiality and SNP heritability of age at onset and episodicity in major depressive disorder. Psychological medicine, 1-11.

Firmann, M., Mayor, V., Vidal, P.M., Bochud, M., Pecoud, A., Hayoz, D., Paccaud, F., Preisig, M., Song, K.S., Yuan, X., Danoff, T.M., Stirnadel, H.A., Waterworth, D., Mooser, V., Waeber, G., Vollenweider, P., 2008. The CoLaus study: a population-based study to investigate the epidemiology and genetic determinants of cardiovascular risk factors and metabolic syndrome. BMC Cardiovascular Disorders 8, 6, 2008.

Ghaemi, S.N., Vohringer, P.A., 2011. The heterogeneity of depression: an old debate renewed. Acta psychiatrica Scandinavica 124, 497.

Glaus, J., Vandeleur, C., Gholam-Rezaee, M., Castelao, E., Perrin, M., Rothen, S., Bovet, P., Marques-Vidal, P., von Kanel, R., Merikangas, K., Mooser, V., Waterworth, D.M., Waeber, G., Vollenweider, P., Preisig, M., 2013. Atypical depression and alcohol misuse are related to the cardiovascular risk in the general population. Acta psychiatrica Scandinavica 128, 282-293.
Goldberg, D.P., 1972. The detection of psychiatric illness by questionnaire. Oxford University Press, Oxford.
Harris, E.C., Barraclough, B., 1998. Excess mortality of mental disorder. The British journal of psychiatry : the journal of mental science 173, 11-53.
Hollingshead, A.B., 1975. Four factor Index of Social Status. Yale University Press.
Ives, D.G., Samuel, P., Psaty, B.M., Kuller, L.H., 2009. Agreement between nosologist and cardiovascular health study review of deaths: implications of coding differences. Journal of the American Geriatrics Society 57, 133-139.
Kessler, R.C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K.R., Rush, A.J., Walters, E.E., Wang, P.S., National Comorbidity Survey, R., 2003. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA : the journal of the American Medical Association 289, 3095-3105.
Lamers, F., Vogelzangs, N., Merikangas, K.R., de Jonge, P., Beekman, A.T., Penninx, B.W., 2013. Evidence for a differential role of HPA-axis function, inflammation and metabolic syndrome in melancholic versus atypical depression. Molecular psychiatry 18, 692-699.
Lasserre, A.M., Glaus, J., Vandeleur, C.L., Marques-Vidal, P., Vaucher, J., Bastardot, F., Waeber, G., Vollenweider, P., Preisig, M., 2014. Depression with atypical features and increase in obesity, body mass index, waist circumference, and fat mass: a prospective, population-based study. JAMA psychiatry 71, 880-888.
Leboyer, M., Barbe, B., Gorwood, P., Teherani, M., Allilaire, J.F., Preisig, M., Matthey, M.L., Poyetton, V., Ferrero, F., 1995. Interview Diagnostique pour les Etudes Génétiques. INSERM, Paris.
Mykletun, A., Bjerkeset, O., Dewey, M., Prince, M., Overland, S., Stewart, R., 2007. Anxiety, depression, and cause-specific mortality: the HUNT study. Psychosomatic medicine 69, 323-331.
Nurnberger, J.I., Jr., Blehar, M.C., Kaufmann, C.A., York-Cooler, C., Simpson, S.G., Harkavy-Friedman, J., Severe, J.B., Malaspina, D., Reich, T., 1994. Diagnostic interview for genetic studies. Rationale, unique features, and training. NIMH Genetics Initiative. Arch Gen Psychiatry 51, 849-859.
Parker, G., Roy, K., Mitchell, P., Wilhelm, K., Malhi, G., Hadzi-Pavlovic, D., 2002. Atypical depression: a reappraisal. The American journal of psychiatry 159, 1470-1479.
Patten, S.B., Williams, J.V., Lavorato, D., Li Wang, J., Khaled, S., Bulloch, A.G., 2011. Mortality associated with major depression in a Canadian community cohort. Canadian journal of psychiatry. Revue canadienne de psychiatrie 56, 658-666.
Preisig, M., Fenton, B.T., Matthey, M.L., Berney, A., Ferrero, F., 1999. Diagnostic interview for genetic studies (DIGS): inter-rater and test-retest reliability of the French version. European Archives of Psychiatry & Clinical Neuroscience 249, 174-179.
Preisig, M., Waeber, G., Vollenweider, P., Bovet, P., Rothen, S., Vandeleur, C., Guex, P., Middleton, L., Waterworth, D., Mooser, V., Tozzi, F., Muglia, P., 2009. The PsyCoLaus study: methodology and characteristics of the sample of a population-based survey on psychiatric disorders and their association with genetic and cardiovascular risk factors. BMC psychiatry 9, 9.
Prusoff, B.A., Merikangas, K.R., Weissman, M.M., 1988. Lifetime prevalence and age of onset of psychiatric disorders: recall 4 years later. Journal of psychiatric research 22, 107-117.
Roberts, R.E., Vernon, S.W., 1983. The Center for Epidemiologic Studies Depression Scale: its use in a community sample. The American journal of psychiatry 140, 41-46.
Rubin, D., 1987. Multiple Imputation for Non-response in Surveys. Wiley, New York.

Ryan, J., Carriere, I., Ritchie, K., Stewart, R., Toulemonde, G., Dartigues, J.F., Tzourio, C., Ancelin, M.L., 2008. Late-life depression and mortality: influence of gender and antidepressant use. The British journal of psychiatry : the journal of mental science 192, 12-18.
Schafer, J.L., 1997. Analysis of incomplete multivariate data. Chapman & Hall CRC, Boca Raton FL [etc.].
Schulz, R., Drayer, R.A., Rollman, B.L., 2002. Depression as a risk factor for non-suicide mortality in the elderly. Biological psychiatry 52, 205-225.
Sterne, J.A., White, I.R., Carlin, J.B., Spratt, M., Royston, P., Kenward, M.G., Wood, A.M., Carpenter, J.R., 2009. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. Bmj 338, b2393.
Surtees, P.G., Wainwright, N.W., Luben, R.N., Wareham, N.J., Bingham, S.A., Khaw, K.T., 2008. Depression and ischemic heart disease mortality: evidence from the EPIC-Norfolk United Kingdom prospective cohort study. The American journal of psychiatry 165, 515-523.
Thase, M.E., 2009. Atypical depression: useful concept, but it's time to revise the DSM-IV criteria. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology 34, 2633-2641.
Udell, J.A., Steg, P.G., Scirica, B.M., Smith, S.C., Jr., Ohman, E.M., Eagle, K.A., Goto, S., Cho, J.I., Bhatt, D.L., Investigators, R.E.o.A.f.C.H.R., 2012. Living alone and cardiovascular risk in outpatients at risk of or with atherothrombosis. Archives of internal medicine 172, 1086-1095.
Van den Akker, M., Schuurman, A.G., Ensinck, K.T.J.L., Buntinx, F., 2003. Depression as a risk factor for total mortality in the community: a meta-analysis. Arch Public Health 61, 313-332.
Vandeleur, C.L., Rothen, S., Lustenberger, Y., Glaus, J., Castelao, E., Preisig, M., 2014. Inter-informant agreement and prevalence estimates for mood syndromes: Direct interview vs. family history method. J Affect Disord 171C, 120-127.
White, I.R., Royston, P., Wood, A.M., 2011. Multiple imputation using chained equations: Issues and guidance for practice. Statistics in medicine 30, 377-399.
Wulsin, L.R., Vaillant, G.E., Wells, V.E., 1999. A systematic review of the mortality of depression. Psychosomatic medicine 61, 6-17.

**Table 1. Baseline characteristics of all participants and according to the presence of a lifetime depressive disorder (DD)**

| | All N=3668 | With DD N=1971 | No DD N=1697 | $X^2$/t | *p* |
|---|---|---|---|---|---|
| Men, % | 47.0 | 36.1 | 59.5 | 200.4 | *<0.001* |
| Age, mean (s.d.) | 50.9 (8.8) | 50.4 (8.7) | 51.5 (8.8) | 3.8 | *<0.001* |
| SES, mean (s.d.) | 3.4 (1.3) | 3.4 (1.3) | 3.4 (1.3) | -0.6 | *n.s.* |
| Living alone, % | 33.1 | 39.3 | 26.0 | 72.6 | *<0.001* |
| Non-Caucasian, % | 8.2 | 8.9 | 7.3 | 3.0 | *n.s.* |
| Anxiety disorders‡, % | 17.9 | 22.7 | 12.4 | 65.1 | *<0.001* |
| Current smoking, % | 28.6 | 30.7 | 26.2 | 9.2 | *<0.01* |
| Alcohol units per week, mean (s.d.) | 6.8 (9) | 5.9 (8.0) | 7.9 (10.0) | 6.7 | *<0.001* |
| Inactivity†, % | 44.2 | 44.1 | 44.4 | 0.0 | *n.s.* |
| Obesity, % | 13.4 | 12.4 | 14.4 | 3.2 | *n.s.* |
| Hypertension, % | 29.9 | 27.3 | 32.8 | 13.3 | *<0.001* |
| Dyslipidemia, % | 32.4 | 30.6 | 34.5 | 6.3 | *<0.05* |
| Diabetes mellitus, % | 5.2 | 4.7 | 5.7 | 2.1 | *n.s.* |
| History of CVD, % | 2.5 | 2.6 | 2.5 | 0.0 | *n.s.* |
| Current antidepressant use, % | 8.3 | 12.6 | 3.3 | 104.2 | *<0.001* |
| Characteristics of DD: | | | | | |
| MDD, % | n/a | 81.7 | n/a | n/a | n/a |
| Atypical features, % | n/a | 16.5 | n/a | n/a | n/a |
| Current , % | n/a | 17.5 | n/a | n/a | n/a |
| Recurrent, % | n/a | 35.4 | n/a | n/a | n/a |
| Time in episodes $\geq$ 1 year, % | n/a | 46.5 | n/a | n/a | n/a |
| Onset < 33 years, % | n/a | 49.0 | n/a | n/a | n/a |

*SES : Socio-economic status according to the Hollingshead Index (5 is highest level), CVD : cardiovascular disease, MDD : Major Depressive Disorder, X2/t: Chi-square test (dichotomous variables)/ t-test (continuous variables), ‡Includes generalized anxiety disorder, social phobia, panic disorder and agoraphobia, †Physical activity during 20 minutes less than twice a week*

**Table 2. Associations between characteristics of depressive disorders and all-cause mortality (N=3668)**

| | Death | Crude HR | | Model 2 | | Model 3 | |
|---|---|---|---|---|---|---|---|
| | % | HR | 95% C.I. | HR | 95% C.I. | HR | 95% C.I. |
| DD characteristics: | | | | | | | |
| *Recency[f]:* | | | | | | | |
| Current | 3.2 | 1.90 | (0.95;3.79) | 3.90* | (1.28;11.91) | 3.23* | (1.05;9.95) |
| Remitted | 0.9 | 0.53* | (0.29;0.98) | 1.06 | (0.42;2.69) | 0.95 | (0.36;2.48) |
| *Diagnostic severity[f]:* | | | | | | | |
| MDD | 1.2 | 0.72 | (0.41;1.27) | 0.66 | (0.24;1.82) | 0.68 | (0.24;1.92) |
| OSDD | 1.7 | 0.95 | (0.39;2.27) | | | | |
| *Atypical features[f]:* | | | | | | | |
| Yes | 1.5 | 0.89 | (0.35;2.3) | 1.22 | (0.45;3.34) | 1.00 | (0.36;2.82) |
| No | 1.3 | 0.74 | (0.42;1.29) | | | | |
| *Recurrence[f]:* | | | | | | | |
| Recurrent | 0.6 | 0.33* | (0.12;0.95) | 0.36 | (0.12;1.11) | 0.38 | (0.12;1.19) |
| Single episode | 1.7 | 0.99 | (0.57;1.72) | | | | |
| *Time spent in episode[f]:* | | | | | | | |
| > 1 year | 1.5 | 0.90 | (0.48;1.69) | 1.23 | (0.50;3.06) | 1.47 | (0.58;3.74) |
| ≤ 1 year | 1.1 | 0.65 | (0.33;1.27) | | | | |
| *Age of onset[f]:* | | | | | | | |
| < 33 years | 0.7 | 0.42* | (0.19;0.96) | 0.76 | (0.30;1.92) | 0.79 | (0.31;2.02) |
| ≥ 33 years | 1.9 | 1.09 | (0.61;1.93) | | | | |
| No DD (ref.) | 1.8 | 1 (ref.) | | | | | |
| Men | 2.2 | 2.39** | (1.36;4.18) | 2.89*** | (1.6;5.23) | 2.17* | (1.14;4.13) |
| Women (ref.) | 0.9 | 1 (ref.) | | | | | |
| Age (cont.) | - | 1.07*** | (1.04;1.11) | 1.79*** | (1.35;2.37) | 1.66** | (1.22;2.26) |
| SES (cont.) | - | 0.93 | (0.76;1.14) | 0.91 | (0.69;1.19) | 0.99 | (0.74;1.31) |
| Living alone | 2.4 | 2.14** | (1.27;3.62) | 2.56*** | (1.49;4.38) | 2.52** | (1.45;4.38) |
| Not living alone (ref.) | 1.1 | 1 (ref.) | | | | | |
| Non-Caucasian | 0.7 | 0.70 | (0.17;2.88) | 0.80 | (0.19;3.33) | 0.75 | (0.18;3.22) |
| Caucasian (ref.) | 1.6 | 1 (ref.) | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| Anxiety disorders‡ | 1.1 | 0.63 | (0.28;1.38) | 0.73 | (0.32;1.65) |
| No anxiety disorders‡ (ref.) | 1.6 | 1 (ref.) | | | |
| Current smoking | 2.9 | 2.82*** | (1.67;4.76) | 2.78*** | (1.59;4.84) |
| Not current smoking (ref.) | 1.0 | 1 (ref.) | | | |
| Alcohol use (cont.) | - | 1.02* | (1.00;1.04) | 0.91 | (0.73;1.13) |
| Inactivity† | 2.2 | 2.17** | (1.27;3.73) | 1.91* | (1.09;3.37) |
| No inactivity† (ref.) | 1.0 | 1 (ref.) | | | |
| Obesity | 2.5 | 1.71 | (0.90;3.24) | 0.89 | (0.43;1.84) |
| No obesity (ref.) | 1.4 | 1 (ref.) | | | |
| Hypertension | 2.7 | 2.53*** | (1.50;4.27) | 1.31 | (0.70;2.44) |
| No hypertension (ref.) | 1.1 | 1 (ref.) | | | |
| Dyslipidemia | 2.5 | 2.36** | (1.40;4.00) | 1.42 | (0.81;2.50) |
| No dyslipidemia (ref.) | 1.1 | 1 (ref.) | | | |
| Diabetes mellitus | 4.8 | 3.55*** | (1.74;7.25) | 1.29 | (0.57;2.93) |
| No diabetes mellitus (ref.) | 1.4 | 1 (ref.) | | | |
| History of CVD | 8.6 | 6.39*** | (3.02;13.51) | 3.50** | (1.54;7.97) |
| No history of CVD (ref.) | 1.3 | 1 (ref.) | | | |
| Current antidepressant use | 1.0 | 0.62 | (0.19;1.99) | 0.45 | (0.13;1.50) |
| No antidepressant (ref.) | 1.6 | 1 (ref.) | | | |

**p<.05; **p<.01; ***p<.001, HR : hazard ratio, 95% C.I.: 95% confidence interval, SES : Socio-economic status according to the Hollingshead Index (5 is highest level), ref. : reference group, cont. : continuous variable, CVD : cardiovascular disease, MDD : Major Depressive Disorder, OSDD : Other Specified Depressive Disorders, ‡Includes generalized anxiety disorder, social phobia, panic disorder and agoraphobia, †Physical activity during 20 minutes less than twice a week. ʃreference group is no DD. Model 2 and Model 3 are proportional hazard models.*

**Table 3. Baseline characteristics of participants with a depressive disorder (DD) according to current or remitted status (N=1971).**

| | Current DD N=345 | Remitted DD N=1626 | $X^2$/t | *p* |
|---|---|---|---|---|
| Men, % | 35.9 | 36.2 | 0.0 | *n.s.* |
| Age, mean (s.d.) | 50.4 (8.3) | 50.4 (8.8) | 0.0 | *n.s.* |
| SES, mean (s.d.) | 3.1 (1.3) | 3.5 (1.3) | 5.0 | *<0.001* |
| Living alone, % | 39.4 | 39.2 | 0.0 | *n.s.* |
| Non-Caucasian, % | 10.7 | 8.5 | 1.8 | *n.s.* |
| Anxiety disorders‡, % | 27.3 | 21.7 | 5.0 | *<0.05* |
| Current smoking, % | 31.9 | 30.4 | 0.3 | *n.s.* |
| Alcohol units per week, mean (s.d.) | 6.0 (9.0) | 5.9 (7.7) | -0.2 | *n.s.* |
| Inactivity†, % | 58.3 | 41.1 | 33.5 | *<0.001* |
| Obesity, % | 16.8 | 11.5 | 7.4 | *<0.01* |
| Hypertension, % | 30.4 | 26.6 | 2.1 | *n.s.* |
| Dyslipidemia, % | 33.0 | 30.1 | 1.2 | *n.s.* |
| Diabetes mellitus, % | 6.7 | 4.2 | 3.8 | *n.s.* |
| History of CVD, % | 2.3 | 2.6 | 0.1 | *n.s.* |
| Current antidepressant use, % | 20.0 | 11.1 | 20.6 | *<0.001* |
| Characteristics of DD: | | | | |
| MDD, % | 91.0 | 79.8 | 24.1 | *<0.001* |
| Atypical features, % | 25.8 | 14.6 | 26.0 | *<0.001* |
| Recurrent, % | 46.1 | 33.1 | 21.0 | *<0.001* |
| Time in episodes ≥ 1 year, % | 76.5 | 40.1 | 151.8 | *<0.001* |
| Onset < 33 years, % | 44.9 | 49.8 | 2.7 | *n.s.* |

*SES : Socio-economic status according to the Hollingshead Index (5 is the highest position), CVD : cardiovascular disease, MDD : Major Depressive Disorder, X2/t: Chi-square test (dichotomous variables)/ t-test (continuous variables), ‡Includes generalized anxiety disorder, social phobia, panic disorder and agoraphobia, †Physical activity during 20 minutes less than twice a week*

**Table 4. Associations between current/remitted status of depressive disorders and cause specific mortality (N=3668)**

| Cause of death | Lifetime depressive disorder | | | | | | No depressive disorder |
|---|---|---|---|---|---|---|---|
| | Current (N=345) | | | Remitted (N=1626) | | | (N=1697) |
| | **N (%)** | HR* | (95% C.I.) | **N (%)** | HR* | (95% C.I.) | **N (%)** |
| Cardiovascular | **2 (0.6)** | 10.91* | (1.02;116.9) | **2 (0.1)** | 0.92 | (0.13;6.46) | **5 (0.3)** |
| Cancer | **5 (1.5)** | 5.07 | (0.96;26.80) | **5 (0.3)** | 1.04 | (0.28;3.92) | **13 (0.8)** |
| Suicide | **1 (0.3)** | 7.33 | (0.24;224.3) | **3 (0.2)** | 4.73 | (0.28;78.70) | **1 (0.1)** |
| Other | **3 (0.9)** | 1.76 | (0.20;15.82) | **5 (0.3)** | 0.77 | (0.14;4.20) | **11 (0.7)** |

**Proportional hazard model adjusted for diagnostic severity, atypical features, recurrence, time spent in episodes, age of onset of depressive disorder, socio-demographics, anxiety disorders, lifestyle characteristics, cardio-metabolic risk factors and diseases and antidepressant use*