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ORIGINAL PAPER

Incident depression and mortality among people with different types of dementia: results from a longitudinal cohort study

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Abstract

Purpose The aim of this study was to investigate the independent and combined association of incident depression and dementia with mortality and to explore whether the magnitude of the association varies according to different types of dementia, including Alzheimer's disease and vascular dementia.

Methods and design The study was based on a population-based longitudinal cohort consisting of 9940 participants at baseline and followed for over 14 years. The sample used for the analyses included 6114 participants with available information on diagnosis of incident dementia and depression. For survival analyses, Cox regression models with incident dementia ($n = 293$; 5%) and incident depression ($n = 746$; 12%) as time-dependent variables were used.

Results Cox models adjusted for relevant confounders indicated that comorbidity of incident vascular dementia and incident depression was associated with a much higher mortality risk (HR 6.99; 95% CI 3.84–12.75) than vascular dementia in the absence of depression (HR 2.80; 95% CI 1.92–4.08). In contrast, estimates for comorbidity of Alzheimer's disease and depression were slightly lower than those for Alzheimer in absence of depression (HR 3.56; 95% CI 1.83–6.92 and HR 4.19; 95% CI 2.97–5.90, respectively). Incident depression in the absence of incident dementia was only weakly associated with mortality.

Conclusions These findings indicate that depression and vascular dementia might have synergistic effects on mortality. The results have relevant public health implications for prevention, routine screening for and early treatment of depression among older people, especially those at risk of vascular dementia.

Keywords Dementia · Alzheimer's disease · Depression · Mortality

Introduction

Depression, especially late-life depression, is a common comorbidity of dementia [1], with significantly higher prevalence of depressive disorders among patients with vascular dementia (VD; 44.1%) than among patients with Alzheimer's disease (AD; 19.5%) or unspecified dementia forms (32.5%) [2].

The relationship between late-life depression and dementia is complex and difficult to disentangle since depression could be a risk factor, a prodromal symptom, or a consequence of dementia. The exact neurobiological mechanisms underlying the comorbidity of dementia and depression are under debate, but evidence suggests that depression in dementia differs from depression in patients without dementia and may derive from anatomic damage to the brain [3] and from neurobiological changes in brain areas common to both pathologies [4]. Several studies support a possible subtype of late-life depression characterized by cerebrovascular

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changes, including white matter lesions, as documented by neuroimaging evidence [5, 6]. Cerebrovascular damage in late-life depression might contribute to explain the findings indicating that late-life depression is more closely related to VD than AD and that individuals with late-life depression, especially those with comorbidity of depression and cognitive impairment, have a higher risk of incident VD than of incident AD [7, 8].

From the observation that dementia and depression are independently associated with damage to the same brain areas, it could be expected that the concurrent occurrence of depression and dementia synergistically increases the burden of both pathologies. This might entail that clinical symptoms of dementia and depression, including disease progression, could be more severe if both pathologies are present compared to each of them alone. Specifically, as dementia is associated with a significantly increased mortality [9], it should be expected that older adults with comorbid dementia and depression have higher mortality than people suffering from dementia alone.

Previous studies observed increased mortality among people with baseline comorbidity of dementia or cognitive impairment and depression [10–13]. However, a comprehensive analysis of the combined and independent associations of incident depression and incident dementia, including analysis by dementia type, with mortality is still lacking. Comparing dementia forms is relevant since depression, especially late-life depression, has a closer relationship to VD than to AD [1, 7, 8], hence the association of comorbid depression and VD with mortality should be stronger than the association of comorbid depression and AD. Also, since there is little evidence concerning mortality among people with depression in the absence of dementia [14, 15], expanding the analyses to incident dementia might contribute to clarifying this issue [16, 17]. Finally, the emphasis on incidence of depression and dementia is important when studying longitudinal cohorts of older people with long-term follow-ups since the likelihood of developing such pathologies, especially dementia, greatly increases with age.

The aim of this study was to assess in a prospective cohort of elderly German people whether comorbidity of incident dementia and incident depression leads to higher mortality risk as compared to each of them alone, and to explore whether the magnitude of the association varies according to different types of dementia, including AD and VD.

Methods

Study participants

The present analyses are based on data from the ESTHER study, a population-based longitudinal cohort study initiated in 2000–2002 in the German state of Saarland. Almost 10,000 participants ($n = 9940$; 55% women) aged 50–75 years were recruited during a general health checkup, which is offered free of charge every 2 years within the German health system to adults older than 35 years. All participants gave written informed consent.

Data collections

All participants filled in a detailed health questionnaire and provided biological samples, including blood samples, which were stored at − 80 °C. General practitioners (GPs) filled in a health questionnaire relating to the participants and, additionally, provided medical records. Biological samples and medical information both from participants and GPs were also collected regularly over the 2-, 5-, 8-, 11-, and 14-year follow-up. The ESTHER study was approved by the Ethics Committees of the Medical Faculty of the University of Heidelberg and of the Physicians' Board of Saarland.

Assessment of dementia

Around the 14-year follow-up, GPs of all ESTHER participants (including those participants who over the follow-up had dropped out of the study because of health reasons or death) were contacted and asked to fill in a detailed questionnaire relating to their knowledge of a possible dementia diagnosis in their patients. If GPs reported a dementia diagnosis they were also asked to provide all available medical records of neurologists, psychiatrists, memory or other specialized clinics that had made the diagnosis of dementia. From the medical records, it could be inferred that the assessment of the dementia diagnosis in the ESTHER population, similar to what occurs in the general population, was heterogeneous [18].

The inclusion of ESTHER participants who had dropped out of the study or deceased was based upon the assumption that most participants with dementia would have already died during follow-up or would not participate actively in the follow-up measurements. Dementia diagnoses were not collected for participants who explicitly withdrew consent to contact their GPs during cohort follow-up ($n = 1121$). Furthermore, dementia diagnoses could not be collected for those participants whose GPs withdrew consent to be contacted during cohort follow-up ($N = 304$) or could not be contacted any more due to other reasons, such as closure of practice, death, or address changes ($n = 1035$). In total, the GPs of 7480 ESTHER participants could be contacted (Fig. 1) and they provided dementia questionnaires for 6422 (86%) participants.

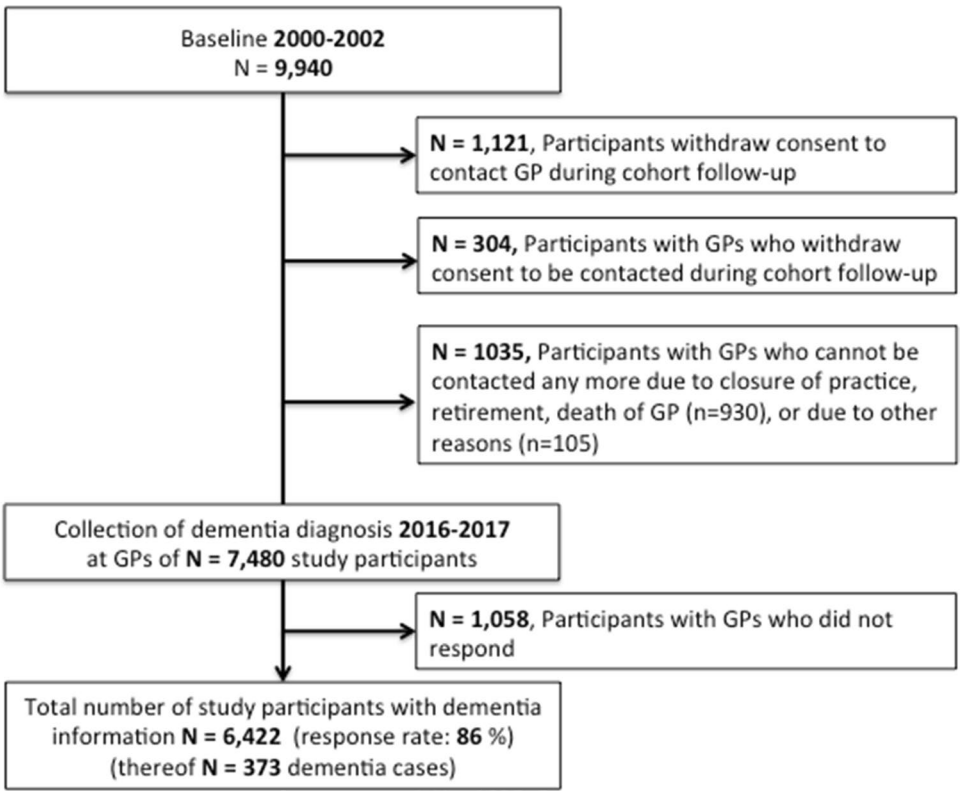

Fig. 1 Flow chart-Collection of dementia diagnoses in the ESTHER study

Assessment of depression

In the baseline health questionnaire participants were asked whether a medical doctor had ever diagnosed them with depression. If they gave a positive answer they were asked to report month and year of the first physician diagnosis of depression. Similarly, in all follow-up questionnaires participants were asked whether they had received a new medical diagnosis of depression since the last questionnaire. In case of a positive answer, they were asked to report the exact date of the diagnosis. In this study, participants with a self-reported medical diagnosis of depression starting from the 2-year follow-up measurement were considered to have incident depression. For patients with recurrent depression, the date of the first depressive episode occurring during the follow-up was considered.

Diagnoses of depression as collected in the ESTHER cohort could not be further differentiated according to subtypes of depression.

Survival status

Mortality follow-up was available until 31 December 2015 and had completeness with respect to loss-to-follow-up of 99.7%. Information on vital status was obtained through inquiry at the residents' registration offices in the total Saarland region and in other German regions for those who moved out of Saarland.

Other covariates

The relevant confounders collected at baseline included sociodemographic factors (age, sex, educational level), lifestyle variables (smoking: never/former vs current smokers, physical activity: inactive, low, medium/high, body mass index; BMI), and lifetime history of diseases common at older age, such as physician reported cardiovascular disease (including myocardial infarction and stroke), diabetes mellitus, and cancer (self-reported and complemented by data from the Saarland cancer registry).

Statistical analysis

Descriptive statistics were used to describe baseline characteristics of the study population and to compare participants with and without dementia information. Differences among participants with and without diagnosis of dementia and with and without information on dementia diagnosis from GPs were investigated with Chi-square test. To assess the association of incident depression or incident dementia or both in reference to the absence of these diseases on overall mortality, Cox proportional hazards models were used. Using incidence data, the exposure status of each patient,

that is (1) coexistence of depression and dementia; (2) presence of dementia but no depression; (3) presence of depression but no dementia; (4) absence of both depression and dementia (reference group), was modeled time-dependently to account for the exact accrued person-times at risk for each exposure status. To realize the time-dependent computing of the four exposure variables (no incidence of dementia or depression, depression, dementia, depression and dementia), the complete follow-up time was split into 6-month intervals and was defined as the date of participant recruitment in the study until death due to any reason, censoring, or end of study period (31 December 2015), whichever occurred first. In this model, patients could have changed between exposure states in each of these 6-month intervals, depending on if the patient was diagnosed with depression or dementia or both in that specific interval or not. This means that a patient could have, for example, first contributed person-time for exposure status (4), absence of dementia and depression, in the first two 6-month intervals and then changed to exposure status (2), dementia but no depression, in case of a dementia diagnosis in the third 6-month interval.

In these analyses, dementia was further differentiated as "all-cause dementia" (ACD), "vascular dementia", and "Alzheimer's disease". ACD included VD, AD, mixed dementia, frontotemporal dementia, and other unspecified dementia forms.

As mortality follow-up (2000–2015) was shorter than the collection period of dementia and depression data, for which questionnaires were returned until end of 2016/beginning of 2017, participants with diagnosis of incident dementia ($n=7$) or incident depression ($n=2$) after the end of mortality follow-up were coded as having no dementia or no depression, respectively.

Additional Cox proportional hazards models were performed after imputing the date of dementia diagnosis for the 47 participants with missing date of diagnosis. Specifically, for these additional analyses the date of dementia diagnosis was imputed using the midpoint of time between baseline and last returned participant questionnaire. Additional Cox proportional hazards models were also performed after participants with either a suspected or unknown diagnosis of dementia were excluded from the total sample of participants without a diagnosis of dementia. All analyses were performed with SAS® version 9.2 (SAS® Institute Inc., Cary, NC, USA).

Results

Among the total number of participants with dementia information from GPs ($n=6422$; Fig. 1) there were 373 (6%) cases with a diagnosis of dementia, thereof 112 (30%) with AD, 129 (35%) with VD, 56 (15%) with mixed dementia, 5 (1%) with frontotemporal dementia, 19 (5%) with "other dementia forms". For 52 (14%) participants the dementia form was not specified ($n=45$) or missing ($n=7$). Additionally, for 108 (2%) participants, the GP reported a suspected diagnosis of dementia and for 288 (4%) the GP was not aware of a diagnosis of dementia.

Participants with dementia diagnosis but missing date of dementia diagnosis ($n=47$) were excluded from the analyses. Out of the remaining 6375 participants, additional participants were excluded because of missing mortality information ($n=4$), missing information from GPs on incident dementia ($n=2$) or incident depression ($n=231$), missing date of baseline questionnaire ($n=2$), implausible date of dementia ($n=15$) or depression ($n=7$). In total 6114 participants remained for the present study.

In this ESTHER sample, there were more women ($n=3343$; 55%) than men ($n=2771$; 45%) (Table 1) and mean age at baseline was around 62 years both among women and men. There were more women than men with incident dementia and, in particular, with AD ($n=53$; 58% and $n=39$; 42%), and with incident depression ($n=473$; 14% and 273; 10%). Mean baseline age was 68 years among participants with incident dementia and 60 years among those with incident depression. The proportion of individuals with lower educational level was higher among those with incident dementia ($n=233$; 80%) than among the total population ($n=4410$; 72%) or people with incident depression ($n=533$; 71%). Baseline prevalence of lifetime history of cardiovascular diseases was much higher among participants with incident VD ($n=23$; 22%) than among participants with incident AD ($n=7$; 8%) or incident depression ($n=83$; 11%).

In the study sample there were 293 (4.8%) incident cases of dementia, thereof 104 (35.5%) with VD, and 92 (31.4%) with AD, and 746 (11.6%) cases of incident depression (Table 2). A higher proportion of participants with incident dementia ($n=54$; 18.4%) than of participants without a certain diagnosis of dementia ($n=692$; 11.9%) reported a medical diagnosis of incident depression. Over the mortality follow-up 1069 (17.5%) participants had died, 142 (48.5%) among those with incident dementia and 122 (16.4%) among those with incident depression.

Participants with and without dementia information had similar prevalence of baseline characteristics but there were statistically significant differences with regard to age, smoking, physical activity, and lifetime history of cancer. Specifically, there was a higher proportion of participants with dementia information who were younger than 65 years, not current smokers, physically active, and a smaller proportion with a lifetime history of cancer (Supplemental Table 1).

Results of Cox models with time-varying exposure states and adjusted for sex, age, and educational level in Model 1 and, additionally, for chronic diseases (cardiovascular

Table 1 Participant baseline characteristics by dementia status (ESTHER cohort study, 2000–2002)

	No dementia diagnosis[a] *N* (%[d])	Vascular dementia *N* (%[d])	Alzheimer's disease *N* (%[d])	Other dementia forms[b] *N* (%[d])	*P* value[c]
Sex					
Women	3193 (55)	57 (55)	53 (58)	40 (41)	0.0585
Men	2628 (45)	47 (45)	39 (42)	57 (59)	
Age					
< 65	3803 (65)	24 (23)	28 (30)	16 (16)	< 0.0001
≥ 65	2018 (35)	80 (77)	64 (70)	81 (84)	
Educational level					
Middle/high[e]	1526 (26)	16 (15)	15 (16)	18(19)	0.0056
Low[f]	4177 (72)	84 (81)	76 (83)	73 (75)	
Lifetime history of depression					
No	4821 (83)	81 (78)	73 (79)	82 (85)	0.5686
Yes	828 (14)	17 (16)	15 (16)	10 (10)	
Lifetime history of cardiovascular disease					
No	5236 (90)	78 (75)	83 (90)	84 (87)	< 0.0001
Yes	440 (8)	23 (22)	7 (8)	9 (9)	
Lifetime history of diabetes mellitus					
No	4909 (84)	77 (74)	70 (76)	72 (74)	< 0.0001
Yes	791 (14)	26 (25)	21 (23)	21 (22)	
Lifetime history of cancer					
No	5414 (93)	98 (94)	83 (90)	89 (92)	0.6704
Yes	407 (7)	6 (6)	9 (10)	8 (8)	
Smoking					
Never/former	4821 (83)	87 (84)	77 (84)	86 (89)	0.0702
Current	878 (15)	15 (14)	12 (13)	5 (5)	
Physical activity					
Inactive[g]	1042 (18)	30 (29)	32 (35)	33 (34)	< 0.0001
Low[h]	2666 (46)	49 (47)	36 (39)	37 (38)	
Medium/high[i]	2102 (36)	25 (24)	24 (26)	26 (27)	
BMI					
< 25 kg/m^2	1624 (28)	27 (26)	34 (37)	26 (27)	0.6289
25–29.9 kg/m^2	2737 (47)	48 (46)	39 (42)	46 (47)	
≥ 30 kg/m^2	1449 (25)	29 (28)	19 (21)	25 (26)	

[a]The group with no dementia diagnosis also includes participants with suspected or unknown dementia diagnosis

[b]Other dementia forms include mixed dementia, frontotemporal dementia, and other unspecified dementia forms

[c]*P* value for comparison among all groups (no dementia diagnosis, vascular dementia, Alzheimer's disease, and other dementia forms)

[d]Percentages are based on the number of participants in the respective group (no dementia diagnosis: 5821; vascular dementia: 104; Alzheimer's disease: 92; other dementia forms: 97). They do not always sum to 100% because of missing values

[e]> 9 years

[f]≤ 9 years

[g]Inactive: < 1 h of physical activity/week

[h]Low: other

[i]≥ 2 h of vigorous and ≥ 2 h of light physical activity/week

Table 2 Incidence of depression according to dementia status in the ESTHER cohort (2000–2015)

	All-cause dementia[a] (*n*, %[c])	Vascular dementia (*n*, %[c])	Alzheimer's disease (*n*, %[c])	No dementia diagnosis[b] (*n*, %[c])
Total number	293 (4.8)	104 (1.7)	92 (1.5)	5821 (95.2)
Incident depression				
Yes	54 (18.4)	19 (18.3)	23 (25.0)	692 (11.9)
No	239 (81.6)	85 (81.7)	69 (75.0)	5129 (88.1)

[a]All-cause dementia includes vascular dementia, Alzheimer's disease, mixed dementia, frontotemporal dementia, and other unspecified dementia forms

[b]The group with no dementia diagnosis also includes participants with suspected or unknown dementia diagnosis

[c]Percentages refer to the total population of 6114 participants

diseases, diabetes mellitus, cancer) and lifestyle factors (smoking, physical activity, BMI) in model 2, are shown in Table 3. A consistent pattern could be observed among ACD and VD cases with the highest mortality risk in the group with both incident depression and incident dementia (HR 4.85; 95% CI 3.18–7.40 and HR 6.99; 95% CI 3.84–12.75, respectively). Mortality risk was also increased in the group with incident ACD (HR 4.15; 95% CI 3.34–5.17) and incident VD (HR 2.80; 95% CI 1.92–4.08) in the absence of depression, but estimates, especially for VD, were lower than in subjects with the incidence of both pathologies. There was no such pattern for AD where hazard ratios for comorbidity of incident AD and incident depression (HR 3.56; 95% CI 1.83–6.92) were even lower than hazard ratios for incident AD in the absence of incident depression (HR 4.19; 95% CI 2.97–5.90). In those with incident depression but no incident dementia, the estimates tended to be only slightly increased.

Results performed with the imputed date of dementia diagnosis remained stable, but both for ACD and VD they showed lower HRs for comorbidity of dementia and depression ($HR_{model\ 2}$ 4.70; CI 3.18–6.94 and $HR_{model\ 2}$ 6.12; CI 3.36–11.15, respectively). For AD the difference between comorbidity of AD and depression ($HR_{model\ 2}$ 4.03;

Table 3 Combined and independent association of depression and dementia with mortality risk (ESTHER cohort, 2000–2015)

Subgroups according to depressive status and dementia forms	Number of person-years in subgroups	Number of deaths (%)[a]	Crude mortality rate per 1000 person-years	Model 1[b] HR for mortality risk	Model 2[c] HR for mortality risk
All-cause dementia (ACD)[d]					
Depression and ACD	175	25 (0.4)	143	5.24 (3.47–7.90)	4.85 (3.18–7.40)
No depression and ACD	800	117 (1.9)	146	4.43 (3.60–5.45)	4.15 (3.34–5.17)
Depression and no ACD	6430	85 (1.4)	13	1.18 (0.94–1.49)	1.13 (0.88–1.43)
No depression no ACD	69,981	715 (11.7)	10	Reference	Reference
Vascular dementia (VD)					
Depression and VD	47	11 (0.2)	234	7.82 (4.30-14.22)	6.99 (3.84–12.75)
No depression and VD	277	34 (0.6)	123	2.93 (2.04–4.22)	2.80 (1.92–4.08)
Depression and no VD	6887	110 (1.8)	16	1.28 (1.05–1.57)	1.23 (0.99–1.52)
No depression no VD	74,228	902 (14.8)	12	Reference	Reference
Alzheimer's disease (AD)					
Depression and AD	88	10 (0.2)	114	3.95 (2.11–7.39)	3.56 (1.83–6.92)
No depression and AD	269	36 (0.6)	134	4.37 (3.12–6.12)	4.19 (2.97–5.90)
Depression and no AD	6870	112 (1.8)	16	1.33 (1.09–1.63)	1.27 (1.03–1.57)
No depression no AD	74,435	910 (14.9)	12	Reference	Reference

HR hazard ratio

[a]Percentages refer to the total number of mortality events in the whole sample ($n = 6114$)

[b]Model 1: adjusted for age, sex, and educational level

[c]Model 2: additionally adjusted for baseline prevalence of chronic disease (cancer, cardiovascular disease, diabetes mellitus) and lifestyle factors (smoking, physical activity, and BMI: continuous)

[d]All-cause dementia includes vascular dementia, Alzheimer's disease, mixed dementia, frontotemporal dementia, and other unspecified dementia forms

CI 2.21–7.36) and AD with no depression ($HR_{model\ 2}$ 4.12; CI 2.98–5.70) was blurring. Results of Cox models performed after the exclusion of participants with suspected or unknown dementia diagnosis remained stable.

Discussion

This study explored the independent and combined association of depression and dementia with mortality risk and compared different dementia forms. The results indicate that the concurrent burden of incident depression and incident dementia is associated with a higher mortality risk than the incidence of dementia alone. This pattern was especially marked for comorbidity of VD and depression but was not observable for AD. Also, this study showed that the incidence of depression in the absence of incident dementia was only weakly associated with increased mortality.

Unique features of this study were the modeling of incident depression and dementia as time-dependent variables and the stratification by type of dementia, which allowed the identification of different patterns among AD and VD. Given the frequent comorbidity of dementia and depression among older people, the finding that coexistence of dementia and depression is associated with a much higher mortality risk has important public health repercussions and it points to the need of improved screening for depression among older people, especially among those at increased risk of VD. This is especially important since depression among older adults is often under diagnosed and under treated or untreated [19].

The mean baseline age of participants developing depression in this study was approximately 60 years or older and the analyses only included new depressive episodes developed over the 14-year follow-up. Hence, it can be inferred that depression in this study refers to late-life depression.

In the ESTHER cohort, the combined effect of depression and dementia was associated with higher mortality for comorbidity for VD but not for AD. This observation might support different neurobiological mechanisms underlying depression in Alzheimer and vascular dementia [20] with a stronger vascular basis of late-life depression in VD than in AD and with depression in AD possibly showing neuropathological and neurobiological pathways specific to AD [4–6]. However, these results do not exclude similar mechanisms of depression in VD and AD with people with comorbidity of VD and depression having a more severe burden of cardiovascular pathologies, inflammation factors or other medical conditions than people with VD without depression [1]. A further explanation for the differences between effects of depression in AD and VD might also be that AD patients with depression are less likely to show aggressive and impulsive behaviour whose pharmacological treatment (especially first-generation antipsychotics and conventional neuroleptics) have been associated with negative side-effects and increased mortality [21].

Other studies exploring the relationship of comorbidity of depression and dementia with excess mortality did not differentiate among different forms of cognitive decline and limited their analysis to baseline prevalence of such pathologies [10, 11, 13]. However, in agreement with the present findings, they all found increased mortality in the presence of comorbidity of depression and cognitive decline. To date, only one study focused specifically on depression and mortality among individuals with incident AD [12] and found that baseline depressive symptoms were significantly associated with mortality among participants with incident, but not with prevalent AD. This supports the reasonableness of the approach of this study to model the incidence of dementia and depression as time-varying exposure states.

The observation relating to small associations of incident depression with mortality in absence of dementia is also in agreement with other studies indicating that the effect of depression on mortality could rather be mediated by later physical health [16]. There is also evidence suggesting that metabolic disorders mediate the association between depression and cardiovascular death [22] and this could contribute to explaining the strong association between depression and death in the presence of VD. Several epidemiological studies summarized in a recent meta-analysis [14] found a significant association between depression and excess mortality, but the examined baseline depression and risk estimates did not include adjustment for incident dementia. However, differences in study designs, in assessment of depression and dementia, in length of mortality follow-up, coupled with the lack of comparability of approaches to data analysis, prevent a full comparison of the present findings with other studies. The suggestion that late-life depression in VD and AD might have different biological substrates resulting in different mortality outcomes needs to be further investigated in future studies with better-characterized dementia cohorts including biomarkers of dementia and neuroimaging for assessment of cerebrovascular pathology.

In the Cox models used for the analyses, the exposure state was carried forward until the end of the follow-up. This approach derives from the chronic condition of dementia, which is an irreversible process. Regarding depression, it could have been possible to allow returning to a previous state but information relating to healing from depression was not available. Further studies with available data on the course of depression should also perform finer analyses allowing the return to a previous state.

ESTHER participants were recruited during a voluntary health check-up, hence they do not reflect a perfect random sample and selection bias might have occurred. However, the distribution of major sociodemographic and risk factors of the ESTHER study population closely resembled that of

a representative German National Health Survey of 1998 and that of other epidemiologic German cohorts [23, 24]. Another possible source of selection bias could be the lack of information on dementia for a large number of ESTHER participants, but since participants with and without dementia information had largely similar prevalence of baseline characteristics and the nonresponse to the dementia questionnaire by GPs was mainly due to reasons related to GPs and not to study participants, the potential for selection bias is reduced.

Other limitations include small numbers of deaths in the subgroup of participants with both dementia and depression, the lack of homogeneity in the assessment of dementia diagnosis, and the self-report of medical diagnosis of depression, which also implies heterogeneity of diagnostic procedures used for diagnosis of depression. While validity of self-reported medical diagnosis of depression has been found to be adequate in another cohort study [25], the possibility of misclassification and recall bias, especially among people with cognitive impairment, cannot be excluded, but it is to be noted that in this study lifetime prevalence of self-reported medical diagnosis of depression is in agreement with estimates reported in other international and German studies [26, 27]. Also, the methodological approach used, with exposure status modeled time-dependently and the splitting of the complete follow-up time into 6-month intervals, contributed to reduce a possible exposure misclassification. However, it remains that the kind of ascertainment of diagnosis of both depression and dementia used in this study could result in underestimation of both conditions.

Modeling of multiple time-varying covariates may cause stratification-collider bias [28], which however is very unlikely in the model used here since both the endpoint (death due to any reason) and one of the independent variables (i.e. incidence of dementia) would need to have a causal effect on the other independent variable (i.e. incidence of depression), which is not possible in this case. Particular strengths of this study include the use of a population-based cohort, the distinction between different types of dementia, the modeling of time-varying covariates, and an appropriate confounder adjustment in Cox models.

In conclusion, these findings show strong associations of comorbidity of late-life depression and VD with mortality and strengthen hypotheses of different patterns for comorbidity of depression in AD and VD. The results highlight the need for further neurobiological studies investigating the specific role of depression in VD and AD and, if confirmed in other studies, also strengthen the need for routine screenings for late-life depression, especially among older people with risk factors for VD.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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