Nuyen J, Spreeuwenberg PM, Beekman AT, Groenewegen PP, van den Bos GA, Schellevis FG.
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Journal of Affective Disorders: 99, 2006, nr. 1-3, p. 73-81

Cerebrovascular risk factors and subsequent depression in older general practice patients

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ABSTRACT

Background: This general practice-based case-control study tested the association between cerebrovascular risk factors (CVRFs) and the development of later-life depression by focusing on the impact of exposure duration to CVRFs and the modifying influence of age at depression onset.

Methods: Cases were 286 patients aged ≥50 years with a first diagnosis of depression at age ≥50 years. Nondepressed controls (*N*=832) were individually matched for age, gender and practice. CVRF diagnoses (hypertension, diabetes mellitus, cardiovascular conditions) prior to depression were determined. Analyses controlled for education, somatic and nondepressive psychiatric disease.

Results: No CVRF variable examined was significantly associated with subsequent depression in the total sample. An unexpected impact of age at onset of depression was observed: the odds ratio associated with having any CVRF was smaller for patients with age at onset ≥70 years than for patients with onset between ages 50–59 years (*p*=.002) and 60–69 years (*p*=.067). Subsequent analyses excluding patients with onset at age ≥70 years revealed that CVRF variables, including long-term exposure to CVRFs, significantly increased the odds of subsequent depression with onset between ages 50 and 69 years.

Limitations: Reliance on GPs' records of morbidity may have resulted in bias towards underestimation in patients with depression onset at age ≥70 years.

Conclusions: Our findings suggest that CVRFs play a relevant role in the development of depression with onset between ages 50 and 69 years, but no evidence was found that they contribute to the occurrence of depression with onset at age ≥70 years. Replication is warranted to exclude the possibility of bias.

1. INTRODUCTION

The vascular depression hypothesis proposes that cerebrovascular disease is an important aetiological factor in late-life depression (Alexopoulos et al., 1997; Krishnan et al., 1997). An implication of this hypothesis is the existence of an association between cerebrovascular risk factors (CVRFs), such as hypertension, diabetes mellitus and cardiac disease, and depression in later life. More specifically, Lyness et al. (1998, 1999) have suggested that the increase in prevalence of CVRFs with age contributes over time to the development of small-vessel brain disease, which, in turn, disrupts neurobiological functioning resulting in depression.

Most studies testing the link between CVRFs and later-life depression have been cross-sectional and used predominantly samples of psychiatric patients. These reports have yielded mixed results (Azar et al., 2005; Baldwin and Tomenson, 1995; Greenwald et al., 1996; Hickie et al., 2001; Lyness et al., 1998, 1999; Krishnan et al., 1995; Mast et al., 2004a; Stewart et al., 2001; Taylor et al., 2004). A major limitation of these studies is their transversal design. Given that depression may also contribute to the development of CVRFs (e.g., Meyer et al., 2004; Van den Akker et al., 2004;Williams et al., 2002; Wulsin and Singal, 2003), it is essential to perform longitudinal studies that specifically address the hypothesized causal pathway of CVRFs leading to the development of depression.

To the best of our knowledge, only two prospective studies have directly examined this association and their results are equivocal. In older primary care patients, Lyness et al. (2000) detected no relationship between baseline severity of CVRFs and depression symptoms and diagnoses at 1-year follow-up after controlling for overall medical burden. Conversely, Mast et al. (2004b) investigated geriatric rehabilitation patients and found an association between a higher number of CVRFs at baseline and the manifestation of depressive symptoms at 6 and 18 months follow-up, also after adjusting for baseline depression scores, limitations in activities of daily living and general medical comorbidity. It is unclear what explains this inconsistency in findings, but differences in patient characteristics may play a role, as well as limitations within the studies. The study by Lyness et al. included patients who were depressed at baseline, rather than focusing exclusively on newly onset depression. Mast et al. examined a specific clinical sample, which was potentially subject to referral bias and focused on a restricted set of three CVRFs (i.e., hypertension, diabetes and atrial fibrillation).

Both longitudinal studies did not examine the impact of the duration of exposure to CVRFs as well as the potential moderating influence of age at onset of depression. Since the theoretical model by Lyness et al. (1998, 1999) postulates that CVRFs produce depression through the development of small-vessel brain disease over time, exposure duration to CVRFs is an essential factor to be taken into consideration. In addition, age at depression onset may modify the relationship between CVRFs and the subsequent development of depression. Given that the prevalence of, and consequently exposure duration to, CVRFs generally will increase with age, one would expect the association between CVRFs and subsequent depression to be stronger in patients with an older age at depression onset compared with patients with a younger age at onset.

The aim of the present case-control study was to further test the association between CVRFs and the subsequent development of depression in older general practice patients. Besides investigating the influences of having any CVRF, specific CVRFs and the number of CVRFs, we examined the effect of exposure duration to CVRFs on the development of depression in later life. In addition, the potential modifying influence of age at depression onset on the relationship between CVRFs and subsequent later-life depression was investigated.

2. METHODS

2.1. Study setting and data

This study was a sub-study of the second Dutch National Survey of General Practice (2001) (Westert et al., 2005) and utilized morbidity data recorded by general practitioners (GPs). In the Netherlands, GPs act as a gatekeeper to health care facilities. After referral, specialists report back results, by which GPs have comprehensive information about the health status of a patient. The majority of Dutch GPs keep electronic medical records of their patients as part of daily medical practice. An important element of these records, initially formulated by Weed (1969), are the so-called “problem lists.” A problem list contains diagnoses of all relevant past and current health problems of a patient, with a health problem defined as “anything that has required, does or may require health care management

and has affected or could significantly affect a person's physical or emotional well-being" (Metsemakers et al., 1992). The dates of establishing the diagnoses are also recorded. Health problems are coded by the GPs according to the International Classification of Primary Care (ICPC) (Lamberts and Woods, 1987) based on the criteria of the International Classification of Health Problems in Primary Care (ICHPPC-2-Defined) (WONCA, 1983).

For the present study, eight practices, comprising 14 GPs, were selected on the basis of their fulfillment of quality criteria relating to the accuracy of dates of diagnoses recorded on the problem lists, as well as the completeness of the registration. These practices took part in a procedure to increase the completeness of the problem lists concerning diagnoses of depressive disorder (ICPC code P76) and heart failure (code K77). This procedure involved running a computer search program that, by searching the entire electronic medical record system for markers (e.g., relevant ICPC codes, certain text strings, specific medication), traced potential cases of depression and heart failure. Subsequently, for each identified possible diagnosis of depression or heart failure, the GP made a decision to add the diagnosis to the problem list.

2.2. Study population

The population registered at the eight practices consisted of 28,307 persons in 2001 and was representative of the Dutch population in terms of age, gender and type of health insurance. The practice population formed the source population.

Cases were defined as patients aged 50 years or older in 2001 who were diagnosed with depressive disorder (ICPC code P76) or depressive feelings (code P03) for the first time at age 50 years or older according to their problem list. The ICHPPC-2- Defined criteria for depressive disorder correspond largely to those of the DSM-IV for major depression (Van den Akker et al., 2004). The P03 code is used for patients with depressive symptomatology who do not fulfill criteria for depressive disorder. Cases diagnosed with stroke or transient ischaemic attack (TIA) and/or dementia before the date of depression diagnosis were excluded (N=20) to minimize the influence of clinically overt cerebrovascular disease and dementia on the relationship between CVRFs and subsequent depression, leaving 286 cases.

Controls comprised those patients who had never received a diagnosis of depression or depressive feelings, but who had at least one other diagnosis on their problem list. This latter requirement was imposed to minimize selectivity due to the degree of attention a GP pays to a patient. For each depressed case, three control patients matched on age (using 5 year age bands), gender and practice were randomly selected. Each matched control was assigned a virtual "exit date" marking the end of the observation period, which was identical to the date of depression diagnosis of the case with whom the control was matched. Controls with a diagnosis of stroke or TIA and/or dementia before the exit date were excluded. A small number of cases were matched to less than three control patients because the number of eligible controls was not sufficient, resulting in 832 control patients.

2.3. Cerebrovascular risk factors (CVRFs)

The current study investigated the following well-established CVRFs (Goldstein et al., 2006; Wolf et al., 1991): hypertension (ICPC codes K86 or K87), diabetes mellitus (code T90) and several cardiovascular conditions, including atrial fibrillation (code K78), chronic ischemic heart disease (code K76), angina pectoris (code K74), myocardial infarction (code K75), heart failure (code K77), and intermittent claudication (code K92). Diagnoses of hypertension, diabetes mellitus, and chronic ischemic heart disease made by GPs have been shown to agree well with the diagnostic criteria of the ICHPPC-2-Defined, with a highest false positive rate of 4% being observed in diabetes mellitus (Schellevis et al., 1993).

For each case (control), the presence of each CVRF diagnosis prior to the date of depression diagnosis (assigned exit date) was determined, as well as the time periods between the date of each CVRF diagnosis and depression diagnosis date (assigned exit date). The influence of the following CVRF variables on the development of subsequent depression was examined: a basic variable "any CVRF" (i.e., any CVRF diagnosis), individual CVRFs (i.e., three CVRF diagnosis categories: hypertension, diabetes mellitus and cardiovascular conditions), the number of CVRFs (i.e., the number of diagnoses belonging to a different CVRF category; possible range=0–3) and the duration of exposure to CVRFs. Regarding this last variable, if a case or control had CVRF diagnoses in more than one category, the time periods between each CVRF diagnosis within the category and depression

diagnosis were summed (e.g., hypertension and diabetes mellitus diagnosed, respectively, 7.7 and 3.0 years before depression diagnosis resulted in a total exposure duration of 10.7 years). Subsequently, this variable was categorized into 0, >0–10, >10–20, and >20 years of exposure. Of note, atrial fibrillation was included in the cardiovascular category and not considered separately because the number of cases with this condition was too small for meaningful analysis.

2.4. Covariates

We took into account other factors that might influence the associations between the CVRF variables and subsequent depression, including attained educational level, other psychiatric disorder and the number of chronic somatic disorders present prior to the development of depression (Krishnan et al., 2002). Educational level was categorized into low (none, elementary school), middle (high school) and high (college or university). Also, a separate category of missing data was created because education data were missing for a substantial number of cases (16.4%) and controls (18.5%). The presence of psychiatric disease was defined as having at least one psychiatric diagnosis other than depression or depressive feelings diagnosed before depression diagnosis date (for cases) or "exit date" (for controls), respectively. The following psychiatric diagnoses were taken into account: anxiety disorders, schizophrenia and other psychotic disorders, and a rest category of other mental disorders. The number of chronic somatic conditions prior to depression was established in a similar fashion, while considering a comprehensive range of conditions relating to various body systems (Nuyen et al., in press). This variable was categorized into four categories, i.e., 0, 1, 2 and ≥3 conditions.

2.5. Statistical analysis

Separate conditional logistic regression analyses were performed using SPSS version 11.5 for Windows (http:// www2.chass.ncsu.edu/garson/PA765/logit.htm) to examine the association between each of the CVRF variables and the subsequent development of depression in the total sample. The potential confounding effects of attained educational level, presence of other psychiatric disease and the number of chronic somatic conditions prior to depression were controlled for in multivariate models.

Next, to examine the potential modifying influence of age at onset of depression, three "age at depression onset" groups were formed consisting, respectively, of cases with depression onset between ages 50 and 59 years (*N*=149) and their matched controls (*N*=439), of cases with onset between ages 60 and 69 years (*N*=70) and their matched controls (*N*=202), and of cases with onset at age 70 years or older (*N*=67) and their matched controls (*N*=191). This categorization was based on the most commonly employed cut-off points, i.e., 50 and 60 years of age, to define late-onset depression (Van den Berg et al., 2001). To investigate whether there existed a different relationship between having any CVRF and subsequent depression for the three age at depression onset groups, an interaction term of any CVRF and age at depression onset group was added to the multivariate model. Interaction was tested by comparing the log likelihood of this model with that of the model without the interaction term (i.e., likelihood ratio test). In case of a significant interaction effect, the odds ratio of developing depression for patients with any CVRF in each of the three age at depression onset groups were assessed using multivariate conditional logistic regression analysis.

Finally, as a sensitivity analysis, all analyses were repeated while excluding cases that were diagnosed with depressive feelings (*N*=16) and their matched controls (*N*=48) to evaluate the effect of possible misclassification of depression. Also, the modifying influence of age at depression onset was examined using a more detailed classification of age at onset groups (i.e., onset between ages 50–54, 55–59, 60–64, 65–69, 70–74 years and onset at ≥75 years) to evaluate the influence of definition of age at onset categorization.

Statistical significance was accepted at the 5% level.

3. RESULTS

Table 1 illustrates the demographic and clinical characteristics of the depressed patients (*N*=285) and their matched controls (*N*=831).

[TABLE 1]

Table 2 shows the results of the conditional logistic regression analyses examining the association between each of the CVRF variables and the subsequent development of depression. None of the CVRF variables was significantly linked to subsequent depression. Additionally controlling for educational level, other psychiatric disease and number of chronic somatic conditions only minimally affected the odds ratios.

[TABLE 2]

Next, the potential modifying influence of age at depression onset on the relationship between having any CVRF and subsequent depression was examined. Noteworthy, the proportion of cases and controls with any CVRF differed across the age at depression onset groups, suggesting a modifying role of age at depression onset. Specifically, in the groups with onset between ages 50 and 59 years (mean age 61.3, S.D. 6.9, 58.9% females) and 60 and 69 years (mean age 70.5, S.D. 5.0; 71.7% females) having any CVRF was more common among cases than controls (22.3% vs. 13.7% and 32.9% vs. 27.7%, respectively). In contrast, in the group with onset at age 70 years or older (mean age 80.3, S.D. 5.9; 80.5% females), a lower proportion of cases than controls had any CVRF (35.8% vs. 46.8%). Indeed, a significant interaction between any CVRF and age at depression onset group (likelihood ratio test: p=.010) confirmed that the influence of having any CVRF differed by age at depression onset group. A subsequent multivariate logistic regression (Table 3) showed that, relative to patients without CVRFs, having any CVRF significantly increased the odds of developing depression in the group with onset between ages 50 and 59 years. In the group with onset between ages 60 and 69 years, having any CVRF also increased the likelihood of subsequent depression, although this relationship was not significant. In contrast, in the group with onset at age 70 years or older, having any CVRF was associated with a significantly decreased odds of developing depression compared to patients without CVRFs. Furthermore, the odds ratio associated with having any CVRF in this oldest age at depression onset group was significantly smaller than that observed in the group with depression onset between ages 50 and 59 years (p=.002) and tended to be significantly smaller than the odds ratio for the group with onset between ages 60 and 69 years (p=.067). The odds ratios associated with having any CVRF did not differ significantly between the two younger age at depression onset groups (p=.31). Using a more detailed classification of age at depression onset yielded essentially similar results.

[TABLE 3]

Given these results, we repeated our analyses concerning the CVRF variables under study while excluding the cases with an age at depression onset of 70 years or older and their matched controls. The demographic and clinical characteristics of the sub-sample are shown in Table 4, and Table 5 presents the regression results.

[TABLES 4-5]

Having any CVRF significantly increased the odds of developing depression with onset between ages 50 and 69 years. Regarding individual CVRFs, the influence of having hypertension tended to be significant in both the bivariate and the multivariate model. Having diabetes significantly increased the likelihood of onset of depression between ages 50 and 69 years, while having any cardiovascular condition did not. Furthermore, a higher number of CVRFs was found to exert a significant effect. Additionally, patients who were exposed to CVRFs for more than 20 years were significantly more likely to have subsequent depression with onset between ages 50 and 69 years than patients who had no exposure to CVRFs. Finally, repeating all analyses after excluding cases with depressive feelings and their matched controls yielded basically similar results.

4. DISCUSSION

In this general practice-based case-control study, none of the CVRF variables examined, including exposure duration to CVRFs, was significantly associated with the subsequent development of depression in later life. In addition, the results refuted our hypothesis that the relationship between having any CVRF and subsequent depression would be stronger in patients with an older age at depression onset compared with patients with a younger age at onset. That is, the odds ratio associated with having any CVRF was significantly smaller in the group with age at depression onset at age 70 years or older than in the group with onset of depression between ages 50 and 59 years and tended to be significantly smaller than the odds ratio observed in patients with onset of depression between ages 60 and 69 years. Subsequent analyses excluding the oldest age at depression onset group showed significant associations between CVRF variables, including long-term exposure duration to CVRFs, and subsequent depression with onset between ages 50 and 69 years. An interpretation of these findings is that CVRFs play a relevant role in the development of depression with onset between ages 50 and 69 years, but that no evidence was found that CVRFs contribute to the occurrence of depression with onset at age 70 years or later.

However, strengths and limitations of the reliance on morbidity data recorded by GPs must be considered when interpreting our findings. A strong point was that the data allowed us to examine the influence of exposure to CVRFs over a lengthy period of time, rather than merely investigating the impact of presence or severity of CVRFs at a given time point. Another strength was that a largely unselected group was studied because almost all non-institutionalized Dutch citizens are registered with a GP. Therefore, potential referral bias was minimal. Furthermore, a possible influence of recall bias concerning onset data was minimized because these were ascertained on the basis of dates of diagnosis recorded by GPs instead of based on patient recall. Relying on GPs' records of morbidity has also limitations.

First, it is likely that the problem lists were not entirely complete regarding diagnoses of depression and CVRFs despite the implemented procedure to increase their completeness. Theoretically, this could have resulted in spurious significant results when the degree of completeness of the recorded CVRF diagnoses was substantially greater among cases than controls. However, we minimized this potential bias towards overestimation by including only controls who had at least one record of a health condition on their problem list. Second, only a limited range of CVRFs could be studied because the available data did not allow us to examine the influence of other risk factors (e.g., smoking, dyslipidemia), though not taking into consideration other CVRFs would most likely have attenuated a true relationship between CVRFs and depression rather than producing a spurious one. Third, examining diagnosis of depression made by GPs and not diagnosis based on a standardized assessment procedure may have led to a substantial misclassification of subjects who actually developed depression as not having had this disorder (i.e., underdiagnosis) and visa versa (i.e., overdiagnosis). At least, the rather low incidence of “depressive feelings” does suggest considerable underdiagnosis of subthreshold depression. If there is a true relationship between CVRFs and depression, misclassification of depression and/or depressive feelings would have resulted in an underestimation of the associations under study, though, in case of differential misclassification, there is also the possibility of overestimating effects. For instance, underdiagnosis of depression may occur less frequently among patients with CVRFs because GPs have raised awareness of depression in these patients. However, we consider this unlikely for two reasons. First, as our study concerned older patients and only control patients were included who had been diagnosed with at least one health problem, the majority of the patients not suffering from CVRFs (i.e., 71%) had at least one somatic disease before the date of depression diagnosis (cases) or assigned “exit date” (controls). Given this high number together with the fact that these health problems in general concern conditions that require health care management and significantly affect a person's physical or emotional well-being (Metsemakers et al., 1992), it is likely that most patients without CVRFs were also subject to increased vigilance by GPs. Second, it remains to be seen whether having CVRFs, or more broadly having a chronic somatic illness, leads to increased detection of depression by GPs. In fact, studies have suggested an opposite effect; that is, they have found that somatically ill patients who have comorbid major depression have a higher risk of not being diagnosed as depressed by GPs than those without a somatic illness (Sartorius et al., 1996; Nuyen et al., 2005). A final limitation of our study is that only patients who were alive at the time of data collection were examined. There is growing

evidence that depression significantly increases the risk of death in adults with diabetes (Zhang et al., 2005), cardiovascular disease (Barth et al., 2004; Wulsin et al., 1999) or hypertension (Simonsick et al., 1995). If so, differential mortality would have resulted in the non-participation of more cases than controls with CVRFs, which, in turn, would have led to an underestimation of the associations under study.

Having addressed potential sources of bias, we cannot rule out the possibility that bias towards underestimation explains the "failure" to find any of the CVRF variables to be significantly associated with the development of later-life depression in our total sample. That is, it is possible that particularly in the oldest age at depression onset group (onset ≥70 years) a significant bias towards underestimation was present because (1) the rate of overdiagnosis and especially underdiagnosis of depression by GPs may be higher in older age groups than among younger age groups (Stek et al., 2004; Volkers et al., 2004), and/or because (2) the mortality rate of patients with CVRFs and comorbid depression may be higher in patients with an older age at depression onset relative to patients with a younger age at depression onset (Philibert et al., 1997). Such pronounced conservative bias in the oldest age at depression onset group could have masked "true" relationships between CVRFs and subsequent later-life depression in our total sample, which only came into sight when this group was excluded from analysis. Further longitudinal research that circumvents the potential biases addressed above is needed to settle the role of CVRFs in the development of depression with onset at age 70 years or older. Anyhow, our findings may help explain why Lyness et al. (2000) did not find significant associations between CVRF variables at baseline and subsequent depression symptoms and diagnoses at 1-year follow-up after controlling for overall medical burden. They examined a sample of primary care patients aged 60 years or older and also conducted separate analyses using a subset of patients with onset at age 60 years or later. However, no analyses were performed excluding patients with depression onset at age 70 years or older.

This is the first study that examined the association between duration of CVRFs exposure over time and the development of later-life depression. We found that patients who were exposed to CVRFs for more than 20 years were significantly more likely to develop depression with age at onset between 50 and 69 years than patients without CVRFs. In the context of the proposed model of Lyness et al. (1998, 1999), this suggests that a long-term exposure to CVRFs is required before they contribute via the development of small-vessel brain disease to the occurrence of depression in later life. It should be noted that our measure of exposure duration to CVRFs weighted each individual CVRF (hypertension, diabetes, cardiovascular disease) equally and also did not take into account treatment of CVRFs. Additionally, in case of exposure to more than one specific CVRF, the exposure duration to each CVRF was simply summed. It is possible that the association between CVRFs and subsequent later-life depression varies with (the exposure duration to an) individual CVRF and that, consequently, each individual CVRF has to be given a specific weight. Our findings concerning specific CVRFs suggest that diabetes and hypertension may play a more important role than cardiovascular conditions in the development of depression in later life. Only a limited number of previous longitudinal studies have examined the association between a specific CVRF and the development of depression and their results are inconsistent (Eaton, 2002; Lyness et al., 2000; Patten, 2001; Polsky et al., 2005). Also, the influence of age at depression onset was not considered in these studies. Further prospective studies are needed to determine whether long-term exposure to CVRFs exerts its effect on the development of later-life depression regardless of type of CVRF or that specific (combinations of) CVRFs do matter.

In sum, although our findings were essentially negative using the total sample of older general practice patients, results of subsequent analyses excluding the patients with onset of depression at age 70 years or older offered support for a longitudinal relationship between CVRFs and subsequent depression in later life. Replication is needed to exclude the possibility that our findings were substantially influenced by biases inherent to relying on morbidity data recorded by GPs. Ideally, such future research should take into account several other variables that appear to moderate the association of CVRFs with later-life depression, including executive functioning (Mast et al., 2004c), severe life stress preceding onset of depression (Holley et al., 2006; Van den Berg et al., 2001) and physical symptoms and limitations (Mast et al., 2005). Ultimately, subgroups of patients could be identified for whom the vascular depression concept is particularly relevant, which, in turn, may guide prevention of depression in later life through modification of CVRFs.

ACKNOWLEDGEMENTS

This study has been supported by a grant from ZonMw "The Netherlands Organisation for Health Research and Development" (CZ-TT 2001). The authors also thank Dr. Joost Janssen (Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht) and Dr. Anita C. Volkers (NIVEL) for their helpful comments.

TABLES

Table 5
Association between cerebrovascular risk factor (CVRF) variables and subsequent depression with onset between ages 50 and 69 using separate conditional logistic regression analyses

	Bivariate		Multivariate	
	OR (95% CI)	p*	OR (95% CI)	p*
Any CVRF	1.61 (1.08–2.39)	.019	1.56 (1.03–2.35)	.034
Individual CVRF				
Hypertension	1.59 (0.99–2.55)	.057	1.57 (0.96–2.55)	.071
Diabetes	2.17 (1.12–4.18)	.022	2.02 (1.03–3.96)	.040
Any cardiovascular condition	1.16 (0.62–2.19)	.64	1.02 (0.53–1.98)	.95
Number of CVRFs (0–2)	1.47 (1.09–1.99)	.013	1.42 (1.03–1.94)	.032
Exposure duration to CVRFs, sum of years				
>0–10	1.45 (0.90–2.32)	.12	1.42 (0.88–2.31)	.15
>10–20	1.36 (0.57–3.26)	.49	1.30 (0.53–3.17)	.57
>20	2.80 (1.20–6.54)	.018	2.64 (1.10–6.35)	.031

Bivariate analysis controlled for the matching variables gender, age and practice. Multivariate analysis additionally controlled for educational level, presence of other psychiatric disease and number of somatic diseases prior to depression.
The reference category for exposure duration to CVRFs is 0 years.
CVRF: cerebrovascular risk factor; OR: odds ratio; CI: confidence interval; *Wald chi-square test.

Table 1
Demographic and clinical characteristics of depressed cases and matched nondepressed controls

Characteristic	Depressed patients (*N*=285)	Control patients (*N*=831)
Mean age (in 2001), years (S.D.) range	68.1 (10.1) 51–92	67.8 (10.0) 51–95
Female gender, *N* (%)	191 (67.0)	557 (67.0)
Educational level, *N* (%)		
High	27 (9.5)	71 (8.5)
Middle	106 (37.2)	337 (40.6)
Low	105 (36.8)	269 (32.4)
Missing	47 (16.5)	154 (18.5)
Other psychiatric disease prior to depression, *N* (%)	30 (10.5)	27 (3.2)
Number of somatic diseases prior to depression, *N* (%)		
0	75 (26.3)	229 (27.6)
1	67 (23.5)	223 (26.8)
2	49 (17.2)	148 (17.8)
≥3	94 (33.0)	231 (27.8)
Any CVRF prior to depression, *N* (%)	80 (28.1)	205 (24.7)
Individual CVRF prior to depression, *N* (%)		
Hypertension	53 (18.6)	131 (15.8)
Diabetes	19 (6.7)	43 (5.2)
Any cardiovascular condition	28 (9.8)	81 (9.7)
Number of individual CVRFs prior to depression, *N* (%)		
1	61 (21.4)	158 (19.0)
2	19 (6.7)	47 (5.7)
Exposure duration to CVRFs prior to depression, sum of years, *N* (%)		
>0–10	55 (19.3)	144 (17.3)
>10–20	9 (3.2)	30 (3.6)
>20	16 (5.6)	31 (3.7)

CVRF: cerebrovascular risk factor.

Table 2
Association between cerebrovascular risk factor (CVRF) variables and subsequent depression using separate conditional logistic regression analyses

	Bivariate		Multivariate	
	OR (95% CI)	*p**	OR (95% CI)	*p**
Any CVRF	1.18 (0.85–1.64)	.33	1.18 (0.80–1.59)	.49
Individual CVRF				
Hypertension	1.23 (0.84–1.80)	.30	1.18 (0.80–1.75)	.41
Diabetes	1.28 (0.73–2.26)	.39	1.20 (0.67–2.13)	.55
Any cardiovascular condition	0.96 (0.60–1.54)	.86	0.85 (0.52–1.40)	.53
Number of CVRFs	1.13 (0.88–1.44)	.34	1.07 (0.83–1.38)	.63
Exposure duration to CVRFs, sum of years				
>0–10	1.15 (0.78–1.69)	.48	1.15 (0.78–1.71)	.48
>10–20	0.91 (0.42–1.96)	.80	0.83 (0.38–1.82)	.65
>20	1.56 (0.82–2.97)	.17	1.32 (0.67–2.60)	.42

Bivariate analysis controlled for the matching variables gender, age and practice. Multivariate analysis additionally controlled for educational level, presence of other psychiatric disease and number of somatic diseases prior to depression.
The reference category for exposure duration to CVRFs is 0 years.
OR: odds ratio, CI: confidence interval, *Wald chi-square test.

Table 3
Association between having any cerebrovascular risk factor (CVRF) and subsequent depression in three "age at depression onset" groups using multivariate conditional logistic regression analysis

	OR (95% CI)	*p**
Any CVRF with age at depression onset 50–59 years	1.88 (1.12–3.14)	.016
Any CVRF with age at depression onset 60–69 years	1.23 (0.64–2.35)	.542
Any CVRF with age at depression onset ≥70 years	0.53 (0.28–0.99)	.045

Analysis controlled for educational level, presence of other psychiatric disease and number of somatic diseases prior to depression.
The reference category is patients without CVRFs.
OR: odds ratio, CI: confidence interval, *Wald chi-square test.

Table 4
Demographic and clinical characteristics of depressed cases with depression onset between ages 50 and 69 years and matched nondepressed controls

	Depressed patients ($N=218$)	Control patients ($N=641$)
Mean age (in 2001) years (S.D.) Range	64.2 (7.6) 51–87	64.2 (7.7) 51–90
Female gender, *N* (%)	137 (62.8)	404 (63.0)
Educational level, *N* (%)		
High	23 (10.6)	66 (10.3)
Middle	91 (41.7)	282 (44.0)
Low	66 (30.3)	176 (27.5)
Missing	38 (17.4)	117 (18.3)
Other psychiatric disease prior to depression, *N* (%)	23 (10.6)	23 (3.6)
Number of somatic diseases prior to depression, *N* (%)		
0	67 (30.7)	198 (30.9)
1	52 (23.9)	187 (29.2)
2	34 (15.6)	116 (18.1)
≥3	65 (29.8)	140 (21.8)
Any CVRF prior to depression, *N* (%)	56 (25.7)	116 (18.1)
Individual CVRF prior to depression, *N* (%)		
Hypertension	36 (16.5)	74 (11.5)
Diabetes	17 (7.8)	24 (3.7)
Any cardiovascular condition	15 (6.9)	37 (5.8)
Number of individual CVRFs prior to depression, *N* (%)		
1	44 (20.2)	97 (15.1)
2	12 (5.5)	19 (3.0)
Exposure duration to CVRFs prior to depression, sum of years, *N* (%)		
>0–10	37 (17.0)	84 (13.1)
>10–20	8 (3.7)	19 (3.0)
>20	11 (5.0)	13 (2.0)

CVRF, cerebrovascular risk factor.

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