VASCULAR HEART AND BRAIN DISEASE AND INCIDENT LATE-LIFE DEPRESSION

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Part I

Introduction

Chapter 1

Introduction

Characteristics of late-life depression

Depression is characterized by depressed mood, loss of interest, rumination, feelings of guilt and shame, suicidal ideation, disturbed sleep and loss of appetite (1). It is associated with limitations in physical and social functioning and places a severe burden on patients and relatives (2).

Compared to depression in middle age, late-life depression has some specific characteristics. Depressive syndromes that escape the strict criteria of the Diagnostic and Statistical Manual of Psychiatric Disorders (DSM) for major depressive disorder and dysthymia are more common in the elderly (3-5). Many elderly have only some symptoms of depression. Such subthreshold depressive syndromes are considered clinically relevant, because they are related to increased disability and mortality, as are depressive disorders that meet DSM criteria (6-10). Moreover, depression is more common in the old age than in midlife. The prevalence ranges from 9 to 18 % in the general elderly population, to more than 30% in long-term care residents (3, 5, 11, 12). Depression in late life often has a chronic course (3, 5, 11, 13) Only 60% of patients recover in one year and 70-80% in two years (7, 9, 14-19).

A number of risk factors for depression has been established, which predispose, precipitate, or perpetuate the disease. Female gender, adverse life events, and poverty are the most well known. Late-life depression has some additional specific risk factors. Depressive symptoms are very much related to cognitive decline, which occur as part of neurodegenerative brain diseases, such as Alzheimer's disease, and Parkinson's disease. Vascular brain damage, such as stroke and white matter lesions, are associated with late-life depression as well. Depression is also common in elderly patients with chronic disabling diseases.

The focus of this thesis is to further assess the association between cardio- and cerebrovascular diseases and depression in late life.

Vascular heart disease and late-life depression

Once, mind, spirit and emotion were thought to center in the heart. That it is the heart which suffers pain and feels anxiety. (Bible Isaiah 65:14, Jeremiah 24:7, Luke 2:19; Rom 5:5; Anonymous writer (Hippocrates?) On the Sacred Disease, c. 425 BCE) In modern times, the relationship between heart and emotional well-being is still topic of many studies (20). Cross-sectional studies show that depression is more common in patients with cardiovascular disease than in the general population (20-23). This was found for heart failure, myocardial infarction and atrial fibrillation. However, little is known about the longitudinal relationship between these diseases and depression. There may be an increased risk of depression in individuals with cardiac disease, an increased risk of cardiac disease in individuals with depression, or both. Only few prospective studies have been performed to test these hypotheses.

Depression has also been associated with medications that are prescribed for these cardiac diseases, such as beta-blockers (24, 25). What is known about the use of cardiovascular medication and the risk of depression has been studied in clinical populations primarily. Moreover, elderly patients are rarely included in randomized trials. Yet, approximately 60% of elderly persons take one ore more of these drugs regularly. A drug-induced depressive disorder would be a preventable or treatable disease in those patients who are vulnerable to this adverse effect, especially because alternative drugs are usually available.

Vascular brain disease and late-life depression

Interest in the relationship between cerebrovascular disease and depression has grown since the early 19th century (26). Atherosclerotic lesions to brain circuits responsible for affective regulation are assumed to form the central mechanism (26-29). Such damage might also affect treatment success and the course of illness. This so called 'vascular depression hypothesis' has been tested primarily in cross-sectional studies. Neuro-imaging and autopsy studies showed that lesions in frontal deep white matter, basal ganglia and gray matter, as well as atrophy were more prevalent in depressed patients than in healthy controls (30). Prospective studies are needed that assess the effect of cerebrovascular risk factors and disease on the risk of incident late-life depression.

Aim and outline

The aim of this research project was to assess whether cardiac diseases, cardiovascular medication, and cerebrovascular disease increase the risk of incident late-life depression in a population-based cohort study.

This thesis is structured as follows. First, data on depressions that occurred newly during follow-up were collected in a population of community-dwelling elderly. We analyzed the rate of new-onset depression in persons without a history of depression (incidence rate) and those with a history of depression (recurrence rate) (Chapter 2). Next, we studied the risk of incident depression related to chronic heart failure and loop-diuretics (Chapter 3), as well as atrial fibrillation (Chapter 4). We went on to assess whether the use of beta-blockers, the most commonly used group of cardiovascular medication, increases the risk of depression (Chapter 5). Subsequently, we examined the longitudinal association between risk factors generally regarded as cerebrovascular risk factors, such as smoking, hypertension and diabetes, and incident depression (Chapter 6). We also assessed the association between the retinal microcirculation, which shares many features with cerebral vessels, and incident depression (Chapter 7). In the next study, vascular brain disease was

visualized with neuro-imaging (Chapter 8). We assessed whether brain atrophy, white matter lesions and brain infarcts predicted the onset of depression. In the final study, we investigated the effect of transient neurological attacks, clinical indicators of atherosclerotic brain disease, on the risk of depression (Chapter 9). The thesis closes with a general discussion of methodology and findings (Chapter 10).

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Chapter 2

Incidence and recurrence of late-life depression

Abstract

Context. Depression is common in old age. Nevertheless, few incidence studies have established how often depression occurs in elderly persons with and without a history of depression.

Objective. To determine the incidence and recurrence rates of depression in an elderly population.

Design. A cohort study performed between 1993 and 2005, encompassing baseline and two follow-up examinations, as well as continuous procedures.

Setting. Community-dwelling elderly persons, aged 56 or older, residing in Rotterdam, the Netherlands.

Participants and data assessment methods. The study population consisted of 5,653 participants free of dementia. Depressions were identified through standardized psychiatric examinations, monitoring of medical records, registration of anti-depressant use, and self-reported histories of depression. We categorized the depressions as depressive syndromes, including DSM-IV defined major depression, or clinically relevant depressive symptoms.

Main Outcome Measure(s). Incidence and recurrence rates for depressive syndromes, as well as for depressive syndromes and symptoms combined. Besides overall rates, sex- and age-specific rates were calculated.

Results. During the follow-up period of 8 years on average, 566 depressive syndromes and 1073 episodes of clinically relevant depressive symptoms occurred. For depressive syndromes, the incidence rate was 7 (95% CI: 6-8) per 1,000 person-years and the recurrence rate was 28 (95% CI: 24-32) per 1,000 person-years. The incidence and recurrence rate more than doubled when episodes of depressive symptoms were included. The recurrence rate of depressive syndromes was equal for women and men, but all other rates were almost twice as high for women compared to men. None of the rates changed with age.

Conclusions. The incidence rate of depression in the elderly is low, except when episodes of clinically relevant depressive symptoms are accounted for. Most late-life depressions occur in persons with a history of depression. Moreover, the recurrence rate of depressive syndromes does not differ between men and women.

Introduction

Depression in old age places a severe burden on patients and relatives, and it occurs frequently.(1-4) Numerous studies have shown that the prevalence of clinically relevant depressive syndromes ranges from 9-18 % in the general elderly population, to more than 30% in nursing home residents.(1-3, 5) To further assess risk and establish risk factors for late-life depression, incidence studies are needed. However, incidence studies that focus on cohorts of elderly persons are scarce.(6, 7) Incidence studies in mixed age populations often involved only small elderly subgroups and were not geared to the specific characteristics of late-life depression.(8-10)

In elderly people, depressive syndromes that escape the strict criteria of the Diagnostic and Statistical Manual of Psychiatric Disorders (DSM) for major depressive disorder (MDD) and dysthymia are more common.(1, 3, 11) Such sub threshold depressive syndromes are often considered clinically relevant, because they are related to increased disability and mortality, like DSM-defined depressive disorders are.(12-15) Therefore, these sub threshold depressions need to be included when estimating incidence rates. Finally, incidence studies to date have typically been based on sequential psychiatric examinations in consecutive follow-up rounds.(2, 9, 10, 16) Depressions that developed and remitted in the interval between follow-up rounds could have easily been missed due to recall problems and loss-to-follow-up.(17, 18) Therefore, methods to identify depressions in the interval period are needed to validly estimate incidence rates.

To our knowledge, two studies have estimated incidence rates of DSM-defined depressive disorders in non-demented elderly cohorts. However, the observed incidence rates varied substantially, ranging between 8 per 1,000 person-years in an American cohort and 23 per 1,000 person-years in a Swedish cohort.(19, 20) Case-finding methods as well socio-economic background of the study populations differed significantly and might explain the difference. Neither of these studies, nor any other population-based study, presented the rate of recurrent depression. Recurrence rates represent the risk of new depressive episodes in persons who already experienced one or more depressions. In clinical studies, 13-88% of elderly patients had a recurrence, depending on whether they received maintenance treatment, and on the duration of follow-up.(21-26) Information on recurrence rates of depression would complement information on incidence rates of new-onset depression in the general population.

Our objective was to determine incidence and recurrence rates of depression in a population-based cohort study of non-demented elderly persons. We used a combination of assessment methods, including continuous monitoring procedures, to identify new-onset depressions.

Methods

Setting

This investigation was embedded in the Rotterdam Study, a prospective population-based study on incidence and determinants of diseases in late life. In 1990, all inhabitants of a district of Rotterdam aged 55 years and over were invited and 7983 agreed to participate (response 78%). (27) The Medical Ethics Committee of the Erasmus Medical Center Rotterdam approved the study and written informed consent was obtained from all participants.

So far, four examination rounds have taken place from 1990-1993, 1993-1995, 1997-1999, and 2002-2004. Participants underwent an extensive home interview and a physical examination at the research centre. Continuous monitoring for major events that occurred during follow-up was achieved through linkage with the medical files from general practitioners. These files contain all medical information as the Dutch health care system requires all residents to be registered with a general practitioner (GP) and specialists report back to the GP. Information on vital status was obtained bimonthly from the municipal authorities in Rotterdam.

Study population

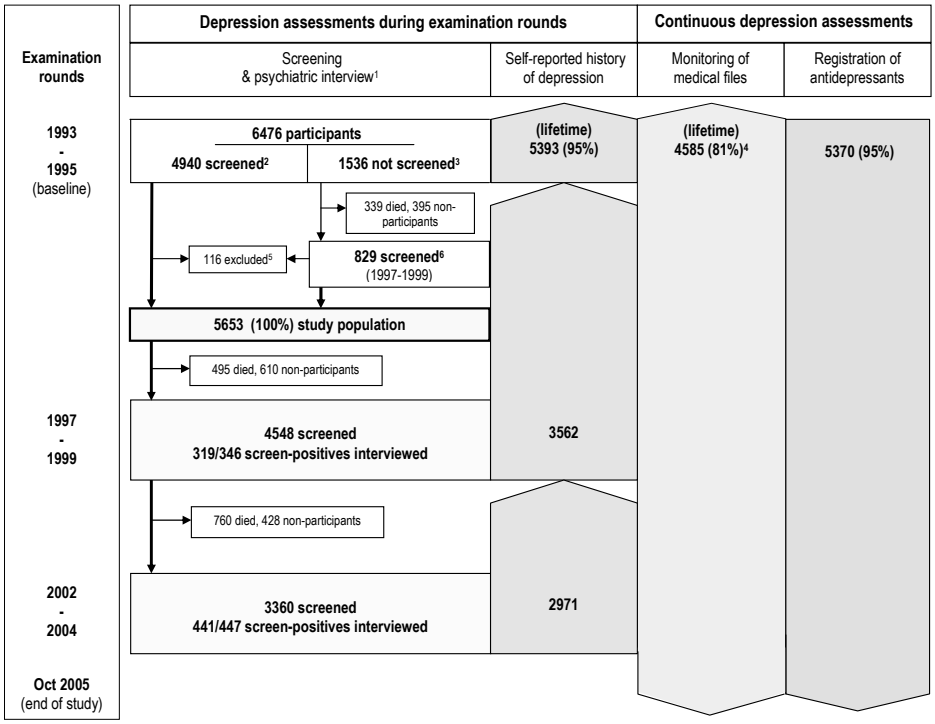
During the first examination round of the Rotterdam Study, 7983 persons participated. Of these participants, 771 died before the second examination round, and 736 were lost to follow-up or refused further participation in any subsequent rounds. In total, 6476 participants participated in the second examination of the Rotterdam Study; this examination constituted the baseline of the present study (figure 1).

Of these 6476 participants, 4940 were screened for depressive symptoms, 1372 did not receive a questionnaire containing the screening instrument for depressive symptoms and 164 did not complete the screening questionnaire. However, 829 of these 1536 non-screened persons were successfully screened in the next examination round. Of the remaining 707 persons, 339 had died before this round and 395 were lost to follow-up or refused further participation. Thus, 5769 persons (4940+829) were screened for depressive symptoms.

We excluded 105 persons with dementia at baseline according to earlier published criteria (28), 9 persons that had been diagnosed with bipolar disorder before or after baseline, and 2 persons who died on the day they had been screened. This resulted in a cohort of 5,653 persons for the analysis.

Persons with dementia were excluded because they cannot report depressive symptoms validly, and without information from primary caregivers, estimates of the incidence of depression in persons with dementia are invalid.(3)

Figure 1 Flow diagram



Assessment of depression

Screening for depressive symptoms was introduced as a pilot project in the Rotterdam Study. At baseline, 48% of the participants filled out the validated Dutch version of the Center for Epidemiologic Studies Depression Scale (CES-D), and 52% the validated Dutch version of the Hospital Anxiety and Depression Scale (HADS).(29, 30) The CES-D consists of 20 questions with possible scores of 0 to 3. A score of 16 or higher on the CES-D is considered indicative of a depressive disorder. 10.5% of participants scored above this cut-off. The HADS contains a subscale of 7 questions on depressive symptoms with possible scores of 0 to 3. We applied ^{3} 9 as the cut-off for the HADS as it yielded a percentage of screen-positives similar to that of the CES-D (9.9%). Among community populations, the sensitivity of the HADS was 90% and the specificity 91%, and that of the CES-D 100% and 88% respectively. (30, 31) In order to enhance case-finding during the follow-up period, information on the occurrence of new-onset depressions was collected with multiple assessment methods.

Psychiatric examination. During the two follow-up rounds, we used a two-step procedure to assess whether participants were going through a depressive episode. First, all participants were screened with the CES-D as part of the home-interview. The screen-positive participants were invited for a clinical interview. A psychiatrist (WO), psycho-geriatrician

(HJL) or clinical psychologist (HJT), each with extensive clinical experience, conducted the interview using the Dutch version of the Present State Examination (PSE-10). This is a semi-structured psychiatric interview included in the Schedules for Clinical Assessment in Neuropsychiatry (SCAN).(32) Scoring of items is conservative and relies on clinical judgment instead of the participant's answer only. Each interviewer was trained in the certified Dutch WHO centre. With a computerized diagnostic algorithm based on the item scores, major and minor depressive disorders and dysthymia were classified according to DSM-IV criteria. The psychiatric examination data were complete for 97% of the participants of the first follow-up round, and 97 % of the participants of the second follow-up round.

Continuous monitoring of medical records. Active surveillance for the occurrence of depressions took place from baseline onward. Trained research-assistants systematically scrutinized all information contained in the medical records of the GPs, for instance hospital discharge letters, specialist reports, and notes of the GP, for a number of predefined cues such as symptoms of depression, prescriptions of psychiatric medication, the occurrence of major life events and psychosocial problems. They copied information that indicated a potential depression. By October 1, 2005, this information was complete for 85% of the follow-up period. Next, two physicians (HL, MD), and a research psychologist (JB) independently read all copied information. They categorized each depression according to a predefined protocol. Instances of bipolar depressive disorder were ascertained as well. All discordant categorizations were discussed in consensus meetings.

Registration of antidepressant drug use. The seven fully computerized pharmacies that serve the study area routinely store information on drugs dispensed to participants in an online database. Ninety-five percent of the participants of the Rotterdam Study fill their prescriptions at one of the pharmacies in the study district. The other 5% either moved out of the study district, or resided in a nursing home that have their own pharmacies. Files were updated from the start of the Rotterdam Study up till October 1, 2005. For this study we used the information on antidepressants to identify potential depressive symptoms or specify the date-of-onset of a depressive episode.

Self-reported history of depression. At baseline and during each follow-up round, all participants were interviewed by a physician to establish their medical history, including depression and certain somatic diseases. Participants were asked standardized questions to assess whether they had suffered from a depression since the previous examination round, and if so whether (s)he had been treated, and at what age the episode had occurred. Baseline data were complete for 95% of the participants.

Categorization of depression

We recorded depressions that fulfilled DSM-IV criteria, as well as depressive episodes that were clinically relevant but that did not meet DSM-criteria. GPs frequently diagnosed depressions without using or documenting the formal DSM-criteria. We applied a cat-

egorization of depression that reflects this variation in severity and diagnostic approach. Our categorization consisted of two categories: depressive syndromes, including DSM-IV depressive disorders, and clinically relevant depressive symptoms.

1- The category depressive syndromes consisted of 'MDD and dysthymia' and 'other depressive syndromes'. 'MDD and dysthymia' encompassed depressive episodes that clearly met the DSM-IV criteria for these disorders. Furthermore, the episodes were diagnosed by a psychiatrist or another mental health professional - be it in specialist health care or by psychiatric interview as part of the Rotterdam Study. The group 'other depressive syndromes' covered a) depression recorded by a GP or physician, b) self-reported depression for which the participant consulted a GP or a mental health professional, and c) DSM-IV minor depression.

2- The category clinically relevant depressive symptoms included a) one clinically relevant core symptom of major depression recorded during the psychiatric interview or in the medical record, b) self-reported depression of a participant who did not consult a GP or a mental health professional, and c) initiation of anti-depressant drug treatment (without documentation of clinical symptoms).

We applied the same criteria to categorize depressions that preceded the study period. Grief, adjustment disorder and burnout, characterized by emotional exhaustion, and reduced satisfaction in personal accomplishment (33), were not regarded depressions.

Recurrent episodes. We assumed that a person had recovered fully if no depressive symptoms had been recorded nor any anti-depressant had been used for a period of at least two years.(34) This two-year criterion not only reflects a conservative approach, but was also deemed appropriate because depression often has a chronic course, with only 60% of patients recovering in one year and 70-80% in two years.(6, 12, 21, 22, 35-38) This way, we took into account that ongoing depressive episodes are frequently poorly documented in primary care medical records, and that a long lag time exists between the onset of a depressive episode and its presentation to a GP. Ideally, actual cessation dates are used, but these are difficult to ascertain in population-based studies.

Date-of-onset. We defined the date-of-onset of a depressive episode as (a) the self-reported date-of-onset as provided in the psychiatric interview or the self-reported history of depression, (b) the first occurrence of a depressive symptom in the medical records, or (c) the day at which the first prescription of an antidepressant drug was dispensed.

Duplicate reports. When an episode was identified with two or more assessment methods, we used the most specific assessment method to determine the diagnosis, i.e. the psychiatric interview overrules the medical records, which in turn overrules the self-reported histories and prescription data. We took the earliest date to define the date-of-onset, with the exception that a date reported retrospectively in the history of depression could not overrule a date from any other assessment method.

Data-analysis

We analyzed incidence and recurrence rates. Persons with no history of depression could experience a *first-ever* depression during follow-up (incidence rate). Persons with a history of depression or prevalent depression at baseline were at risk of a *recurrent* depression (recurrence rate).

First, we calculated the incidence and recurrence rate of all depressions combined, including MDD, dysthymia, other depressive syndromes and clinically relevant depressive symptoms. The incidence rate was calculated in 3,459 participants who did not have depressive symptoms at baseline nor a history of depression, and who were therefore at risk of a first-ever depression. The recurrence rate was calculated in a total of 2,753 participants who were at risk of recurrent depression: 1,645 participants had a positive history of depression and 549 participants had a prevalent depression at baseline; 559 participants were at risk after they had experienced a first-ever episode during follow-up.

Secondly, we calculated incidence and recurrence rates of depressive syndromes only, including MDD and other depressive syndromes. For this analysis the first follow-up examination served as baseline, because this was the first round during which prevalent depressive syndromes were formally diagnosed (N=4,343). There were 3,461 participants who were at risk of a first-ever depression, and 1,158 participants at risk of a recurrent depression. In addition, we calculated the incidence and recurrence rate of MDD and dysthymia in this study population.

All rates were obtained by dividing the number of new-onset episodes by the number of person-years at risk. Participants were censored when one of the following events occurred: dementia, death, loss-to-follow-up, or October 1, 2005 (end of the study). Individuals did not contribute person-time to the analyses of the recurrence rates as long as they used antidepressants, nor during the two years after the last prescription. . Age-specific rates were calculated per 10-year age-stratum (<65, 65-74, 75-84, >85) for men and women separately. The 95% confidence intervals were based on the Poisson distribution. Female-to-male ratios for the rates were calculated using Cox' proportional hazards analysis adjusted for baseline age. To assess the impact of the two-year criterion in our definition of a recurrent episode, we recalculated the recurrence rates using a one- and a three-year criterion.

Finally, we compared the 736 persons who refused to participate at baseline to the 6476 responders. Similarly, we compared the 1536 participants who were not screened in the 1993-1995 baseline examination round to the 4940 screened participants.

Results

At baseline, the study population consisted of 2,945 (59%) women and 2,159 men. The mean age was 70 years (range of 56 to 102 years), 63 % of the participants were married or living together, and 20% had primary school only. The participants lived independently (97%) or in an assisted living facility (3%). In total, 1,744 persons died during the follow-up period. The mean follow-up period was 8.0 years.

In the follow-up period, 2,093 new-onset depressions were identified. After discarding 454 duplicate reports, 1,639 episodes remained. Table 1 displays the number of episodes that were identified with each assessment method. All methods contributed considerably to the number of episodes identified. Of these episodes 174 were categorized as MDD or dysthymia, 392 as another depressive syndrome, and the remaining 1,073 as clinically relevant depressive symptoms. Two-thirds of the episodes (1080) involved recurrent episodes. 216 persons experienced more than one episode during the follow-up period.

Table 1 Number of depressions by assessment method (n= 5,653)*

Assessment method	Depressive syndromes		Depressive symptoms	All depressive episodes (%)
	MDD and dysthymia	Other depressive syndromes		
Psychiatric examination	133	83	178	394 (24)
Medical records	41	89	122	252 (15)
Self-reported history	NA	220	115	335 (20)
Anti-depressant use	NA	NA	658	658 (40)
Total	174	392	1073	1639 (100)

* Only unique episodes are reported. When duplicate reports existed the episode is reported under the most accurate assessment method. For instance, 35 duplicate reports of depressive syndromes in medical records were ignored. MDD stands for major depressive disorder according to DSM-IV criteria; NA stands for not applicable.

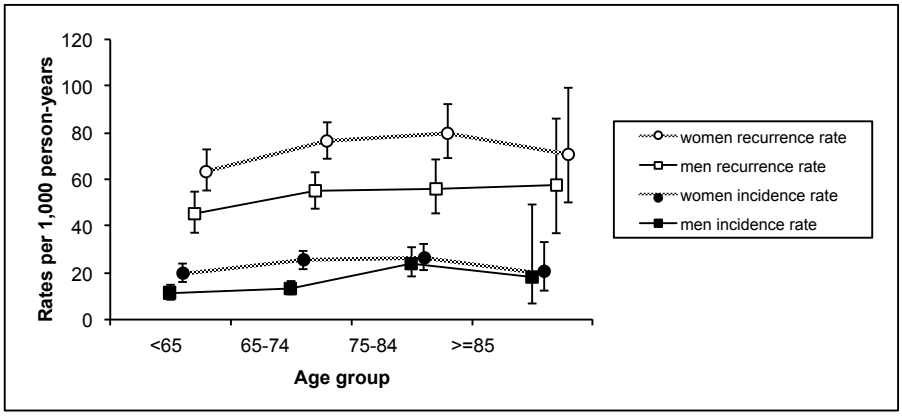
Table 2 presents the overall and sex-specific incidence and recurrence rates for episodes of depressive syndromes and clinically relevant depressive symptoms combined. The overall incidence rate was 19.3 per 1,000 person-years (95% CI: 17.8-21.0). The Cox' proportional hazards regression generated an age-adjusted female-to-male ratio of 1.56 (95% CI: 1.31-1.86). The recurrence rate was 65.6 per 1,000 person-years (95% CI: 61.8-69.7). Thus, the rate of any new-onset depression in participants with a positive history is more than three times higher than the rate in participants with no history. The age-adjusted female-to-male ratio was 1.39 (95% CI: 1.21-1.59) for the recurrence rate. Figure 2 shows that the incidence and recurrence rates appeared to be relatively stable across 10-year age groups.

Table 3 shows the overall and sex-specific incidence and recurrence rates for depressive syndromes only. The overall incidence rate was 7.0 per 1,000 person-years (95% CI: 6.0-

Table 2 Overall and sex-specific incidence and recurrence rates of episodes of depressive syndromes and depressive symptoms combined per 1,000 person-years

		Cases	Person-years	Rate	95% CI
Incidence (n=3,459)	Men	198	13500	14.7	12.8-16.9
	Women	361	15431	23.4	21.1-25.9
	Overall	559	28932	19.3	17.8-21.0
Recurrence (n=2,753)	Men	295	5712	51.6	46.1-57.9
	Women	785	10745	73.1	68.1-78.4
	Overall	1080	16457	65.6	61.8-69.7
Total		1639	45389	36.1	34.4-37.9

Figure 2 Incidence and recurrence rates of episodes of depressive syndromes and symptoms combined per age group



8.3). Using Cox' regression, we found an age adjusted female-to-male ratio of 1.95 (95% CI: 1.49-2.56). The overall recurrence rate was 27.5 per 1,000 person-years (95% CI: 23.7-32.1). The female-to-male ratio was 1.18 (95% CI: 0.84-1.65). Similarly, incidence and recurrence rates appeared to be relatively stable across 10-year age groups.

The incidence rate for MDD and dysthymia was 2.1 (95% CI: 1.6-2.8) per 1,000 person-years, with a female-to-male ratio of 2.44 (1.47-4.06). The recurrence rate was 10.2 per 1,000 person-years (95% CI: 8.0-13.0), with a female-to-male ratio of 0.95 (0.56-1.60). The rates were relatively stable with age.

Table 3 Sex-specific and overall incidence and recurrence rates of depressive syndromes per 1,000 person-years

		Cases	Person-years	Rate	95% CI
Incidence (n=3,461)	Men	40	8932	4.5	3.3-6.1
	Women	107	11990	8.9	7.4-10.8
	Overall	147	20922	7.0	6.0-8.3
Recurrence (n=1,158)	Men	47	1914	24.6	18.5-32.7
	Women	120	4149	28.9	24.2-34.6
	Overall	167	6063	27.5	23.7-32.1
Total		314	26985	11.6	10.4-12.9

When re-estimating the recurrence rates using a one- and three-year criterion instead of a two-year criterion for the definition of a recurrent episode, the overall rate for all episode combined changed from 65.6 (95% CI: 61.8-69.7) to 76.9 (95% CI: 73.0-81.1) and 60.8 (95% CI: 57.0-64.8) per 1,000 person-years, respectively. Likewise, the overall rate of 27.5 (95% CI: 23.7-32.1) for depressive syndromes only, became 30.1 (95% CI: 26.2-34.6) using a one-year and 21.0 (95% CI: 17.4-25.4) per 1,000 person-years using a two-year criterion.

Non-participants at baseline were on average older (75.8 versus 68.6 years), and more likely to be female (70% versus 60%) and have primary school education only (39% versus 23%). The 1536 participants who were not screened in the 1993-1995 round did not differ from the 4940 participants who were screened for depressive symptoms at that time.

Discussion

In this study of community-dwelling elderly persons, incidence rates were 19 per 1,000 person-years for first-ever depressive syndromes and clinically relevant depressive symptoms combined, and 7 per 1,000 person-years for depressive syndromes only. However, most episodes occurred in persons with a history of depression, with recurrence rates being more than three times as high as incidence rates. In women, as compared to men, the incidence and recurrence rate of depressive syndromes and symptoms combined were almost twice as high, but women and men had similar risks of a recurrent depressive syndrome.

Before discussing our findings, we point out the strengths and weaknesses of our study. First, this is a large study population with a long follow-up time, which enhances the accuracy of the estimates. Second, in order to overcome recall problems, we combined several assessment methods to enhance the detection of incident cases. During the follow-up rounds an extensive psychiatric assessment was applied, and a self-reported history of depression was recorded. As older patients are less likely to acknowledge having affective symptoms (39), we chose the CES-D as screening instrument; it has been validated in elderly populations, and yields small numbers of false-negatives when using a cut-off of 16.(30, 40) The SCAN interview method has a high sensitivity compared to the DIS and CIDI, especially in elderly populations, and provides accurate DSM-IV defined diagnoses. (41-43)

Furthermore, we identified depressions that occurred between the follow-up rounds by monitoring medical records and registration of antidepressant use. The major advantage of these prospectively gathered data is that recall and selection bias are reduced. People tend to forget or undervalue past depressions, and report only those episodes that occurred in the five years preceding the assessment.(18, 44) Moreover, as depression is related to mortality

and loss-to-follow-up, episodes will be missed especially in elderly persons.(12) However, abstracting diagnoses from medical records also has some limitations. The information in the records is recorded for the purpose of patient care, not for epidemiological research. Symptoms of depression may have been incompletely recorded or omitted. Even though we applied a broad range of cues that indicate depression, this drawback cannot be fully overcome. Moreover, depression often remains unrecognized, as many elderly patients tend to present somatic complaints masking emotional symptoms.(35, 45-47) General practitioners diagnose between 30 to 60% of depressions, with lower recognition for more milder cases.(48-50) However, when a general practitioner diagnoses a depression, this probably reflects actual depressions(51), but the reports of other health professionals to the GPs were often elaborate with substantiated DSM-classified diagnoses.

Automatic registration of filled prescriptions not only has the advantages of prospective methods, the data are also particularly useful to specify the date-of-onset of episodes. In some etiological studies, antidepressant use is used as an indicator of a depressive syndrome.(52, 53) However, modern antidepressants are commonly prescribed for other indications such as anxiety disorders, sleeping disorders, migraine, or neuropathic pain. (54, 55) Population surveys and family practices studies have shown that 43-56% of patients receiving an antidepressant do not fulfill the criteria of depression.(54, 56-58) Hence, we regarded antidepressant use as a marker of depressive symptoms only.

The psychiatric assessment during the examination rounds yielded more valid diagnoses than the other methods. The main rationale for using data from other sources, albeit with different diagnostic certainty and reliability, was to identify the depressive episodes that occurred and remitted in the intervals between follow-up examination rounds. Information from the different sources is thus additive. At the same time, many depressions successfully with antidepressants are not recalled and certainly not screened positive if assessed only with the CES-D. In addition, depressions for which a participant has not sought help will have been missed more easily. The category 'clinically relevant depressive symptoms' probably covers the most diverse types of depression. One core symptom of major depression recorded in the psychiatric interview or in the medical record, was considered a sufficiently valid indication of the presence of 'clinically relevant depressive symptoms'. In addition, even though the use of an anti-depressant drug provides less diagnostic certainty, it indicates a depression in 50% of users.(54, 56-58)

Our study yielded lower incidence rates than those presented by other studies in elderly populations. In our study the incidence rate for major depression and dysthymia was 2 per 1,000 person-years (95% CI: 2-3), while the Cache County study presented an incidence rate for major depression of 8 per 1,000 person-years (95% CI: 6-11). To some extent, this higher incidence rate is explained by the diagnoses of depression that were made in interviews with family and caregivers of deceased participants (20% of total). Similarly, in our study the incidence rate for depressive syndromes, including major depression,

dysthymia and minor depression, was 7 per 1,000 person-years (95% CI: 6-8), whereas the Göteborg study yielded an incidence rate for major depression, dysthymia and depression NOS of 23 per 1,000 person-years (95% CI: 18-29). This study differed from ours in that it was performed more than 20 years ago in a relatively small birth cohort of 322 persons born in 1901-1902. Most likely though, our lower estimates resulted from our conservative approach in categorizing depressive episodes as being a depressive syndrome. In addition, our study population may have included fewer participants with misclassified negative histories, because data was available on the occurrence of depression in the period between the start of the study and the first follow-up examination, which served as baseline for our analysis of depressive syndromes. Indeed, the incidence rate of depressive syndromes and symptoms combined that we found seems more in line with that of the abovementioned Cache County study: 19 per 1,000 person-years (95% CI: 18-21) compared to 24 per 1,000 person-years (95% CI: 20-27) respectively.(20) In particular as 20% of the depression cases in the latter study involved bereavement. Finally, some studies have found that late-life depression is more often characterized by somatic and cognitive symptoms, even though others found no differences.(59-62) As the conventional core symptoms of depression in the DSM are important for our categorization, the incidence and recurrence rates that we present are probably conservative estimates.

Some landmark studies performed among mixed-age populations in North-America and Scandinavia, such as the Epidemiologic Catchment Area Study, the Lundby Study, and the Stirling County Study have also estimated incidence rates of major depression in the elderly subgroups. The most recently published analyses show incidence rates for major depression between 0.9 and 4.5 per 1,000 person-years.(8-10) We found an incidence rate for major depression and dysthymia of 2 per 1,000 person-years (95% CI: 2-3). The results seem similar to ours, even though in the cited studies psychiatric assessments were generally based on the DIS, intervals between follow-up rounds were much longer (11 to 40 years), continuous monitoring during the intervals was generally lacking, and demented participants were not excluded.

In the present study we found particularly high recurrence rates for both depressive syndromes and clinically relevant depressive symptoms, even though we discounted all events occurring within two years of the previous episode. To our knowledge, no other study to date has estimated recurrence of depression in a general elderly population. In clinical elderly populations, the risk of recurrence increased with the number of lifetime episodes and decreased as the duration of recovery increased.(21, 63, 64) A few population-based studies, all conducted in predominantly middle-aged adults, consistently found that about half of the depressed persons had a recurrence if followed for longer periods.(38, 65, 66) Our study showed that the recurrence rates of MDD and dysthymia were five times as high as the first ever incidence rates in later life. This suggests that clinicians must not only be aware that many depression in later life will be chronic or recurrent but that few

depressive episodes diagnosed are first ever episodes. This emphasizes the importance of maintenance treatment and close monitoring after recovery from depression.

We found that men had similar risks for a recurrent depressive syndrome as women, even though the female-to-male ratios of the other rates that we studied were in line with the well-known ratio of 1.5-3.0.(67, 68) In adult populations no significant sex differences in the course of major depressive disorder were found as well.(65, 69) Prospective studies among adult populations have shown rather consistently that psychological and social risk factors such as higher levels of anxiety, lower self-confidence, lack of power, role strain and sexual abuse contribute to the higher risk of first-ever depression in women.(70, 71) In addition, men seem to recollect less episodes of depression and underreport the severity of symptoms compared to women.(72, 73) Studies that investigated gender differences in late-life depression are scarce. One study suggested that depressed older men were less likely to endorse core depressive symptoms or to be referred for treatment.(74) Apparently, risk factors for incident depressions do not always predict the course of depression as well. The risk factors for recurrent late-life depression are possibly less gender related, and recurrent depressive syndromes might be as easily recognized in men as in women.

In conclusion, if a person has never had a depression in middle age, his risk of developing a first-ever episode in old age may be lower than estimated before. Conversely, if someone has experienced a depression before, the risk of a recurrent episode in old age is high. In fact, the majority of new episodes in our study were recurrent episodes. These findings, in addition to the chronic nature of depression, could explain the well-known discrepancy between the high prevalence and low incidence of late-life depression. Community-dwelling elderly persons have a much higher risk of developing a recurrent than a first ever depression. To enhance diagnostic accuracy, it is thus important that clinicians become aware of this a priori risk. More research is needed to clarify the etiology of recurring late-life depression, given that recurring episodes contribute substantially to the impact of depression on public health.

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Part II

Vascular heart disease and late-life depression

Chapter 3

Heart failure

Abstract

Background. Depression is common in patients with heart failure and associated with recurrent cardiac events and increased mortality. It is still unclear whether heart failure is a risk factor for developing depression. The aim of this study was to determine the association between heart failure and incident depression, and assess whether the use of loop diuretics in persons with heart failure alters this risk.

Methods. We performed a cohort study between 1993 and 2005 among 5,095 elderly inhabitants of Rotterdam, the Netherlands. They were free of depression at baseline. Detailed information on heart failure and depression was collected during examination rounds, and through continuous monitoring of medical and pharmaceutical records. Heart failure was defined according to the criteria of the European Society of Cardiology. Depressive episodes were categorized as depressive syndromes, including DSM-IV defined major depressive disorder, or clinically relevant depressive symptoms. We used multivariate Cox' proportional hazard regression to calculate hazard ratios (HR).

Results. Heart failure was associated with an increased risk of depressive symptoms and syndromes combined (HR 1.41; 95% CI 1.03-1.94). It also increased the risk of depressive syndromes (HR 1.66; 95% CI 1.09-2.52). In participants with heart failure, the use of loop diuretics more than halved the risk of depressive symptoms and syndromes (HR 0.46; 95% CI 0.22-0.96) and depressive syndromes only (HR 0.41; 95% CI 0.16-1.00).

Conclusions. Heart failure is an independent risk factor for incident depression in elderly persons. Effective treatment of the debilitating symptoms of heart failure may prevent depression.

Introduction

High rates of depression among patients with heart failure have been reported in numerous studies.(1) Depression is present in one out of five patients with heart failure. The proportion rises to one out of three patients if episodes of depressive symptoms that do not meet the criteria of major depression are included. Moreover, the prevalence of depression increases with the severity of heart failure (11% in New York Heart Association Class I vs. 42% in Class IV). Co-morbid depression in heart failure complicates effective treatment. It is associated with a greater than 2-fold risk of recurrent cardiac events and mortality.(1-4) This finding is consistent for subthreshold and major depressions. In addition, depression in heart failure is associated with significant increases in functional disability and health care utilization.(5)

The high rates of depression in heart failure in cross-sectional studies (1, 2, 6, 7) might be explained by an increased risk of heart failure in individuals with depression, by an increased risk of depression in individuals with heart failure, or by both. Only few studies have investigated the temporal relationship between heart failure and depression. The risk of incident heart failure in depressed patients varied from a hazard ratio of 1.5 in a general elderly population followed for 14 years (8), to 2.6 in a group of patients with systolic hypertension followed for 4.5 years.(9) To our knowledge, no study has investigated whether heart failure is associated with an increased risk of developing depression. Differentiating between already existent and incident depression in patient with heart failure can be of clinical importance. For example, in myocardial infarction only incident depression is associated with an impaired cardiovascular prognosis, not already prevalent depression.(10)

Undoubtedly, a life event such having a failing heart, which is potentially fatal, might lead to depression in a patient. Moreover, heart failure is associated with impaired daily functioning, a known risk factor for depression.(11) A biological link might be that reduced cardiac output as a result of heart failure could lead to insufficient cerebral perfusion. Loop-diuretics, which are often prescribed for heart failure, deplete circulating volume and thus decrease blood pressure even further.(12-14) On the other hand, loop diuretics effectively diminish the debilitating symptoms of heart failure, and might decrease the risk of depression.

Prior studies that examined heart failure as a risk factor for depression have been limited by their cross-sectional design and clinical study population. The aim of this population-based study was to estimate the effect of heart failure and loop-diuretics on the risk of incident depression in the elderly. Detailed information on heart failure and depression was collected for 5,095 participants during on average eight years of follow-up.

Methods

Setting

This study was part of the Rotterdam Study, a prospective study that started in 1990 among 7,983 inhabitants of Ommoord, a district of Rotterdam.(15) The participants were 55 years of age or older at that time. The study focuses on the occurrence and determinants of common chronic diseases in the elderly. The Medical Ethics Committee of the Erasmus Medical Center Rotterdam approved the study and written informed consent was obtained from all participants.

So far, four examination rounds have taken place (1989-1993, 1993-1995, 1997-1999, and 2002-2004). Participants underwent an extensive home interview and a physical examination at the research centre. Blood was drawn and electrocardiography (ECG) was carried out. In addition, continuous monitoring for major cardiovascular and psychiatric events took place through automated linkage with the medical files from the general practitioners (GPs) from baseline onwards. The Dutch health care system requires all residents to be registered with a GP, and clinicians report back to the GP. Furthermore, the pharmacies that serve the neighborhood provided complete online information on all filled prescriptions for virtually all participants. This information included the Anatomical Therapeutic Chemical code; total number of delivered units (e.g. tablets/capsules); prescribed daily number of units; date of delivery and drug dosage. Finally, information on vital status was obtained bimonthly from the municipal authorities in Rotterdam.

Study population

During the second visit, the baseline of the current analysis, 5,769 participants were screened for depressive symptoms. Participants filled out either the validated Dutch version of the Center for Epidemiologic Studies Depression Scale (CES-D) or the validated Dutch version of the Hospital Anxiety and Depression Scale (HADS-D).(16, 17) A score of 16 or higher out of 60 on the CES-D and 9 or higher out of 21 on the HADS-D was considered screen-positive for depressive symptoms.(16, 17) At baseline, we excluded 549 persons with depressive symptoms, 105 persons with dementia (18), 9 persons with bipolar disorder diagnosed before or after baseline, 9 persons with missing heart failure status and 2 persons who were lost-to-follow-up on the day they had been screened. This resulted in a study population of 5,095 persons who were free of depression at baseline.

Assessment of incident depression

The assessment of depression in the Rotterdam Study has been described in detail before. (19) Information on the occurrence of incident depressions during follow-up was obtained from (1) psychiatric examinations, (2) self-reported histories of depression, and (3) medical records. The psychiatric examination consisted of a two-step procedure during

examination rounds. First, all participants were screened with the CES-D as part of the home-interview. Next, the screen-positive participants were invited for a clinical interview, in which trained clinicians administered a semi-structured psychiatric interview included in the Schedules for Clinical Assessment in Neuropsychiatry (SCAN).(20) Major and minor depressive disorders and dysthymia were ascertained with a computerized algorithm that reflected DSM-IV criteria.(21) The self-reported history of depression was solicited at baseline and during follow-up rounds. Participants were asked standardized questions to assess whether they had suffered from a depressive episode up to that time, and if so whether they had been treated, and at what age the episode had occurred. The GPs' medical records were scrutinized by trained research-assistants. They copied the information that indicated a potential depression. Two research physicians independently assessed this information, and categorized each depressive episode according to a predefined protocol (see below).

Based on these sources, we categorized depressive episodes into depressive syndromes, and clinically relevant depressive symptoms. The category 'depressive syndromes' consisted of major depressive disorder and dysthymia that clearly met the DSM-IV criteria for either of these disorders, and that were diagnosed by a psychiatrist or other mental health professional. The category also covered other depressive syndromes, that is depression recorded by a GP, self-reported depression for which the participant consulted a health professional, and DSM-IV minor depression. The category 'clinically relevant depressive symptoms' included a report of one core symptom of major depression in the psychiatric interview or medical record, and self-reported depression without consultation of a health professional. We applied the same criteria to categorize depressive episodes that preceded the study period.

We defined the date-of-onset of as the day of the reported first occurrence of symptoms of depression, or the first prescription date of an antidepressant drug (tricyclic antidepressants, (non)selective serotonin reuptake inhibitors, or other), whichever came first.

Assessment of heart failure

The assessment procedures for heart failure have been described in detail previously.(22, 23) In brief, during the first examination round of the Rotterdam Study, information on the presence of symptoms and signs of heart failure and the use of medication for heart failure was obtained.(23) Additionally, virtually all medical records of GPs were screened for the occurrence of incident cases of heart failure during follow-up.(22) Furthermore, a database with discharge diagnoses from the hospitals in the Rotterdam area was linked to the study database, and copies of discharge letters of potential cases were requested. Two research physicians independently classified the information and discussed all differing classifications in a consensus meeting. Finally, a cardiologist judged decisively about the probable and discordant cases.

Definite heart failure was defined as a combination of (1) the presence of at least one of the typical signs or symptoms of heart failure, i.e. breathlessness at rest or during exertion, ankle oedema and pulmonary crepitations, and (2) confirmation of cardiac dysfunction on chest X-ray or echocardiography. Symptoms could not be attributed to another underlying disease, such as chronic obstructive pulmonary disease. This definition is in accordance with the criteria of the European Society of Cardiology.(24) For definite heart failure, the diagnosis had to be ascertained by a medical specialist. A case was classified as probable when a medical specialist' diagnosis was missing, but two or three typical symptoms suggestive of heart failure were present, as well as a history of cardiovascular disease (e.g., myocardial infarction, hypertension), response to treatment for heart failure, or objective evidence of cardiac dysfunction. The current study is based on probable and definite cases of heart failure.

The date-of-onset was defined as the day of the first reported occurrence of symptoms of heart failure, or the first prescription date for a loop diuretic or angiotensin-converting-enzyme-inhibitor, whichever came first.

Covariates

The following baseline characteristics were considered as potential confounders of the association between heart failure and depression: age, sex, socio-economic status, disability in activities of daily living, history of depression, smoking, hypertension, and history of ischemic heart disease. In addition, as dates-of-onset had been ascertained, diabetes mellitus, myocardial infarction, atrial fibrillation, and use of loop diuretics and (other) antihypertensive medication could be included as time-varying covariates.

Socio-economic status was determined in terms of highest education attained and net income.(25) Disability in activities of daily living was assessed with the Modified Stanford Health Assessment Questionnaire.(26) This scale ranges between 1.0 and 4.0 and higher scores represent more disability. Self-reported smoking was categorized into never, former, and current. For blood pressure, the average of two measurements in sitting position at the right upper arm with a sphygmomanometer, was used for our analysis. Hypertension was defined as diastolic blood pressure of 100 mmHg or above, or systolic blood pressure of 160 mmHg or above (27), or the use of antihypertensive drugs for the indication hypertension. History of ischemic heart disease encompassed angina pectoris and claudicatio intermittens, both established with the Rose questionnaire, as well as a history of coronary artery bypass graft, percutaneous transluminal coronary angioplasty and peripheral artery bypass graft.

The criteria for diabetes mellitus were: fasting plasma glucose level of ≥ 7.0 mmol/l, non-fasting glucose or an oral glucose tolerance test result of ≥ 11.1 mmol/L, or treatment with an antidiabetic medication or diet.(28) A history of myocardial infarction was defined as self-reported myocardial infarction confirmed by information from medical

records, or an ECG characteristic of prior myocardial infarction according to the ICD-10 (code I21) as verified by a cardiologist.(29) A diagnosis of atrial fibrillation according to ICD-10 (code I48) required an ECG that verified the diagnosis.(30) The medical or pharmaceutical records yielded the date-of-onset of these events.

Information on the use of loop diuretics and other antihypertensive medication was obtained from the pharmaceutical database. The other antihypertensive medication included low-ceiling diuretics, beta-blockers, angiotensin-converting-enzyme-inhibitors, reserpine, methyldopa, and clonidine. The duration of a prescription was calculated as the total number of delivered units divided by the prescribed daily number of units. Thus, we were able to distinguish between non-use and current use on the index date if this date fell within a prescription period.

Statistical analysis

To study the effect of heart failure on the risk of incident depression, we performed a Cox' proportional hazard analysis. Heart failure was entered in the model as a time-varying exposure variable. We performed the analysis with the outcome depressive symptoms and syndromes combined, as well as depressive syndromes only. (Given the low number of depressive disorders, we expected insufficient power for this outcome.) We fitted two multivariate models for both outcomes. In the first model, we adjusted for age and sex only, in the second additionally for all other confounders. Next, we reran the two models in the subsample of persons without a history of depression at baseline to estimate the risk of first-ever incident depression. In this way, we further reduced bias due to reversed causality in the estimated association between heart failure and depression. Finally, in order to assess the effect of loop diuretics on the risk of depression, we compared the risk of depression in current users to that in non-users in the participants with heart failure. In these analyses we included the same co-variates, except diabetes, because it is not a (contra-)indication for use of loop diuretics.

In all of the analyses, the participants contributed person-years from the date of the baseline interview until follow-up ended either when a depression occurred or when a participant was censored due to dementia, death, loss-to-follow-up, or the end of the study on October 1, 2005. Missing values for the baseline covariates were imputed using the last observation carried forward, i.e. the measurements from the first examination round of the Rotterdam Study. For the variables income and hypertension, means were imputed and, to adjust for the potential confounding effect of these imputations, dummies that indicated the missing values were included in the multivariate models. Two-sided p-values of <0.05 were considered statistically significant. For all statistical analyses we used SPSS for Windows, version 15.0.

Results

Table 1 presents the baseline characteristics of the study sample. The average age was 70 years with a range of 56 to 101 years and 58 % of the participants were female. The most prevalent cardiovascular risk factor was history of smoking with 51% former smokers and 17 % current smokers. At baseline, 1641 participants had a history of depression, and 206 participants had heart failure. Another 423 persons developed heart failure after baseline during follow-up. In our study population, a total of 736 incident depressions occurred during 42,090 person-years. Of these depressions, 407 were depressive syndromes, including 103 DSM-defined major depressive disorders and dysthymias. The mean time between onset of heart-failure and onset of depression was 3.5 years (SD 2.9), counting cases of heart failure present at baseline from that time onward.

Table 1 Baseline characteristics of the study population (N=5,095)

Characteristic	Descriptives
Socio-demographic factors	
Age, mean (SD)	70.0 (8.3)
Female, n (%)	2939 (57.7)
Education, primary school only, n (%)	934 (18.3)
Income, mean (range), in euros/month	1220 (350-3200)
Cardiovascular risk factors	
Smoking	
- former smoker, n (%)	2598 (51.0)
- current smoker, n (%)	868 (17.0)
Hypertension, n (%)	1140 (22.4)
Diabetes, n (%)	537 (10.5)
Cardiac disease	
Heart failure, n (%)	206 (4.0)
Myocardial infarction, n (%)	348 (6.8)
History of other ischemic heart disease*, n (%)	1006 (19.7)
Atrial fibrillation, n (%)	430 (8.4)
Other health related factors	
Disability in ADL†, mean (SD)	1.3 (0.6)
History of depression, n (%)	1641 (32.2)
Medication use	
Loop diuretics, n (%)	223 (4.4)
Other antihypertensive medication, n (%)	1505 (29.6)
Digoxin, n (%)	235 (4.6)

* This encompasses a history of angina pectoris, claudicatio intermittens, coronary artery bypass graft, percutaneous transluminal coronary angioplasty and peripheral artery bypass graft. † ADL stands for activities of daily living.

Figure 1 depicts the Kaplan-Meier survival curves by heart failure status. After 12 years of follow-up, twice as many participants with heart failure had developed depression than

those without heart failure. A similar difference was seen for depressive syndromes only. Table 2 shows the risk of depression associated with heart failure. Heart failure was associated with a significantly increased risk of depressive symptoms and syndromes combined (HR 1.36; 95% CI 1.03-1.81) and depressive syndromes only (HR 1.54; 95% CI 1.06-2.24) when age and sex were the sole factors adjusted for. The risk estimates were similar, that is 1.41 (95% CI 1.03-1.94) for depressive symptoms and syndromes and 1.66 (95% CI 1.09-2.52) for depressive syndromes, in the models that adjusted for all confounders and the associations remained significant.

Figure 1 Kaplan-Meier curves of depression-free survival by heart failure status

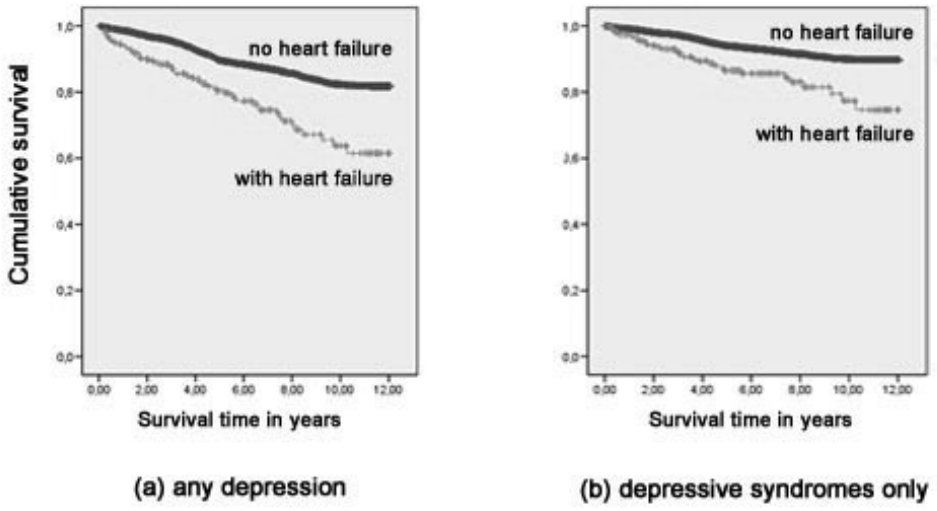

Table 2 Heart failure and the risk of depression estimated with Cox' regression

	Depressive symptoms and syndromes†		Depressive syndromes only‡	
	HR (95%CI)	p-value	HR (95%CI)	p-value
Complete sample (n=5,095)				
Heart failure, age and sex adjusted	1.36 (1.03-1.81)	.033	1.54 (1.06-2.24)	.024
Heart failure, fully adjusted*	1.41 (1.03-1.94)	.036	1.66 (1.09-2.52)	.019
Persons without history of depression (n=3,454)				
Heart failure, age and sex adjusted	1.41 (0.93-2.13)	.103	1.79 (1.05-3.04)	.033
Heart failure, fully adjusted*	1.64 (1.04-2.58)	.033	2.07 (1.15-3.72)	.015

* adjusted for age, sex, SES, ADL, history of depression, smoking, hypertension, diabetes, myocardial infarct, history of other ischemic cardiovascular
disease, atrial fibrillation, and use of loop diuretics and other antihypertensive medication.
† episodes of clinically relevant depressive symptoms and depressive syndromes, including DSM-defined depressive disorders, combined.
‡ includes DSM-defined depressive disorders

Next, we estimated the risk of first-ever incident depression in the persons without a history of depression at baseline (n=3,454). In the multivariate model, heart failure again carried an increased risk of depressive symptoms and syndromes (HR 1.64; 95% CI 1.04-2.58), and depressive syndromes (HR 2.07; 95% CI 1.15-3.72). Moreover, persons with heart failure had a three-fold, almost significant, risk of first-ever depressive disorders (HR 3.00; 95% CI 0.86-10.50; not in table) compared to the others.

Table 3 presents the risk of depression related to the use of loop diuretics in persons with heart failure. In the models adjusted for age and sex only, current use of loop diuretics was not significantly associated with depressive symptoms and syndromes (HR 0.59; 95% CI 0.30-1.15), nor with depressive syndromes only (HR 0.48; 95% CI 0.22-1.06). However, the multivariate models indicated similar but just significant associations for both outcomes, with a more than 50% reduced risk of depressive symptoms and syndromes (HR 0.46; 95% CI 0.22-0.96) and depressive syndromes only (HR 0.41; 95% CI 0.16-1.00) in current users of loop diuretics.

Table 3 Current use of loop diuretics and risk of depression in persons with heart failure (n= 629)

	Depressive symptoms and syndromes†		Depressive syndromes only‡	
	HR (95%CI)	p-value	HR (95%CI)	p-value
Diuretic use, age and sex adjusted	0.59 (0.30-1.15)	.122	0.48 (0.22-1.06)	.068
Diuretic use, fully adjusted*	0.46 (0.22-0.96)	.039	0.41 (0.16-1.00)	.050

* adjusted for age, sex, SES, ADL, history of depression, smoking, hypertension, myocardial infarct, history of other ischemic cardiovascular disease, atrial fibrillation, and use of other antihypertensives.

† episodes of clinically relevant depressive symptoms and depressive syndromes, including DSM-defined depressive disorders, combined.

‡ includes DSM-defined depressive disorders

Discussion

The present study demonstrates that people with heart failure had an increased risk of developing incident depression. The risk remained similarly high when persons with a history of depression were excluded. Our findings also suggest that the use of loop diuretics in persons with heart failure decreased the risk of incident depression. Many cross-sectional studies have shown that depression is very common in heart failure. Our study demonstrated that heart failure is also a risk factor for incident depression. To the best of our knowledge, there is only one other prospective study. It showed that 21% of 245 outpatients with heart failure had depressive symptoms one year later.(31) Patients living alone, reporting alcohol abuse, perceiving medical care as an economic burden, and those with impaired health status were more likely to develop depressive symptoms. However, the lack of a control group forestalled a conclusion about the risk of incident depression in that study.

Heart failure is a fatal disease, with only 35%-50% of patients surviving more than 5 years.(22, 32) Experiencing the symptoms of such a life-threatening disease may provoke a psychological reaction, and when coping mechanisms fail, a patient may become depressed. Reversely, individuals with high levels of perceived self-control are better able to manage their cardiac disease, which in turn leads to improvement of functional status and thereby to a decrease in depression.(6) In addition, biological mechanisms might explain the increased risk of depression related to heart failure. For instance, reduced cardiac output as a result of heart failure could lead to insufficient cerebral perfusion and the drugs prescribed for it may cause hypotension, dizziness and fatigue that may in turn lead to psychological discomfort.(14) In the current study, use of loop diuretics was associated with a protective effect against depression. As loop diuretics effectively diminish the debilitating symptoms of heart failure, this finding suggests that the symptoms of the disease themselves may account for the increased risk of depression. Finally, evidence exists of a common genetic vulnerability for risk factors of heart failure, such as atherosclerosis and myocardial infarction, and depression.(33)

Our study was based on a large population-based cohort and long follow-up period. It is unlikely that information bias occurred in our study. Data were gathered prospectively and without prior knowledge of the research hypothesis. In addition, detailed information on the occurrence of heart failure and depression was collected. As heart failure and depression show some overlap in symptoms, such as lack of energy and listlessness, clear and mutually exclusive definitions needed to be used.(2) The core symptoms of heart failure and depression in our case definitions did not include any overlapping symptoms. Moreover, the results of the analyses based on a more stringent definition of depression (depressive syndromes only) remained significant despite the smaller number of cases. This is suggestive of a true increase in risk. However, the dates-of-onset of heart failure and depression need to be precise. For both diseases, we used all available information from interviews, prescriptions, and medical records. Given that the mean lag-time between the onset of heart failure and the onset of depression was more than three years, we consider it unlikely that pre-existent depressions were taken for incident depressions in our study, even if they had a long prodromal period. Moreover, when we performed the analyses in the participants without a history of depression in order to further reduce this type of misclassification, the results did not change substantially.

A potential source of selection bias might be that patients with heart failure died before their depression was diagnosed and recorded. Depressions in terminally ill patients are often not diagnosed or recorded by the treating physician.(34) We have probably missed some of these episodes. However, this would have led to an underestimation of the true risk and it would mean that our risk estimates are conservative.

We minimized potential confounding by adjusting for a considerable number of socio-demographic and health related factors. However, some confounding by severity of heart failure

might have occurred, because we did not have baseline information such as left ventricular systolic function. Current users of loop diuretics probably have more severe heart failure than non-users, and the prevalence of depression increases with the severity of heart failure.(1) This would have resulted in an underestimation of the protective effect of loop diuretics.

Recently, clinicians have begun to pay greater attention to the treatment of co-morbid depression in patients with cardiovascular disorders such as heart failure, because depression confers an increased risk of recurrent cardiac event and mortality. The present study shows that heart failure is also associated with a more than two-fold increased risk of *new-onset* depression. Our findings additionally emphasize the need for effective interventions to prevent depression in patients with heart failure. As, in our study, the use of loop diuretics seemed to protect heart failure patients against the development of depression, somatic and psychological treatments with a focus on improvement of functional status might prove effective.

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Chapter 4

Atrial fibrillation

Abstract

Objective. In cross-sectional studies, atrial fibrillation (AF) is common in depressed patients, but whether AF causes depression is unclear. We assessed whether AF increases the risk of incident late-life depression.

Methods. In 4,750 elderly persons from the Rotterdam Study, detailed information on the occurrence of AF and depression was collected between 1993 and 2005. AF was identified by electrocardiography. We categorized depressive episodes as clinically relevant depressive symptoms or as depressive syndromes including DSM-IV defined depressive disorders. We calculated hazard ratios with multivariate Cox regression.

Results. AF was not associated with an increased risk of depressive symptoms and syndromes combined. It was associated with depressive syndromes (HR 1.63; 95% CI 1.04-2.55) when adjusted for age and sex, but this association lost statistical significance when adjusted for all confounders (HR 1.49; 95% CI 0.94-2.37).

Conclusions. In this prospective study, AF was not an independent risk factor for incident late-life depression.

Objective

Depressive symptoms occur frequently in the elderly, and even more frequently in patients with atrial fibrillation (AF), the most common cardiac arrhythmia. In a study among 101 patients with AF, 38% had depressive symptoms, which typically had persisted more than 6 months.(1) Also, patients with major depression have AF and related conductive abnormalities on electrocardiography (ECG) more often than healthy controls.(2-4)

Little is known about the temporal relationship between AF and depression. It has been suggested that AF increases the risk of depression because disturbances of heart rate and heart-rate variability have consequences for blood flow to the brain, and may interfere with brain function.(5) Alternatively, stroke and heart failure, the major causes of morbidity in patients with AF, can give rise to depression. To our knowledge, AF has not been studied as a risk factor for incident depression before. The aim of this prospective study was to assess the association between AF and late-life incident depression.

Methods

Setting

This study was part of the Rotterdam Study, a population-based cohort study that started in 1990 among 7,983 inhabitants of Rotterdam, aged ≥ 55 years.(6) The Medical Ethics Committee of the Erasmus Medical Center Rotterdam approved the study and all participants provided written informed consent. So far, four visits have taken place in which participants underwent a home interview and physical examination.

Study population

During the second visit, the baseline of the current analysis, 5,769 participants were screened for depressive symptoms. Participants filled out either the validated Dutch version of the Center for Epidemiologic Studies Depression Scale (CES-D) or the validated Dutch version of the Hospital Anxiety and Depression Scale (HADS-D). A score of 16 or higher out of 60 on the CES-D and 9 or higher out of 21 on the HADS-D was considered screen-positive.(7) At baseline, we excluded 549 persons with depressive symptoms, 105 with dementia, 9 with bipolar disorder, 2 who were lost to follow-up directly after screening, and 354 persons with unknown AF status. This resulted in a study population of 4,750 persons, who were free of depression at baseline.

Assessment of incident depression

Information on incident depressions was obtained from (1) psychiatric examinations, (2) self-reported histories of depression, and (3) medical records.(7) The psychiatric

examination during follow-up visits consisted of a screening with the CES-D, and in the screen-positive participants a semi-structured interview performed by a trained clinician (Schedules for Clinical Assessment in Neuropsychiatry). The self-reported history of depression, solicited during the visits, included standardized questions to ascertain whether and when participants had had a depressive episode, and if they had been treated. To continuously monitor incidence of depression throughout follow-up, trained research-assistants scrutinized the medical records of the general practitioners (GPs) and copied the information about a potential depression. Two research physicians independently assessed this information according to a predefined protocol, and discussed discordant assessments.

We categorized the depressive episodes into (1) depressive syndromes, including DSM-defined major depressive disorder and dysthymia, and other depressive syndromes, such as depressions recorded by a GP, self-reported depression for which a health professional had been consulted, and DSM-IV minor depression; or (2) 'clinically relevant depressive symptoms', if at least one core symptom of major depression had been reported.

We defined the date-of-onset as the day of the first report of symptoms, or the first prescription date of an antidepressant drug, whichever came first.

Assessment of atrial fibrillation (AF)

AF was ascertained using 3 methods.(8) (1) At baseline and during follow-up visits, ECGs were recorded and analyzed with the Modular ECG Analysis System. Two research physicians blinded to the MEANS diagnosis recoded all ECGs with a diagnosis of AF, atrial flutter, or any other rhythm disorder independently. A cardiologist's judgment was decisive in those cases in which disagreement persisted between the coding physicians. (2) Medical records were also screened for the occurrence of AF by research assistants. A senior physician examined the information that had been copied. (3) Information on AF was acquired from the National Medical Registration system, which accumulates validated discharge diagnoses of all Dutch hospitals.

A diagnosis of AF according to ICD-10 (code I48) required an ECG that verified the diagnosis. We did not distinguish between AF and atrial flutter, or between paroxysmal AF and chronic AF. If AF was identified from the medical files, the earliest date was considered the date of onset. If AF was detected exclusively during one of the follow-up rounds, the midpoint between the date of that round and the date of the previous round was taken.

Covariables

The following baseline characteristics were considered as potential confounders: age, sex, socio-economic status, disability in activities of daily living, history of depression, smoking, hypertension, diabetes, history of ischemic heart disease, myocardial infarction, heart failure, stroke, transient ischemic attacks, and use of antihypertensive medication .

Statistical analysis

We performed a Cox' proportional hazard analysis for the outcome 'depressive symptoms and syndromes together', and depressive syndromes only. A multivariate model with all confounders mentioned above was fitted for each outcome. The models were repeated in the subsample of persons without a history of depression at baseline. In this way, we further ascertained the chronological relationship between AF and depression.

In all analyses, the participants contributed person-years from baseline until follow-up ended, either when a depression occurred or when a participant was censored due to dementia, death, loss-to-follow-up, or the end of the study on October 1, 2005. Two-sided p-values of <0.05 were considered statistically significant. For all statistical analyses we used SPSS for Windows, version 16.0.

Results

At baseline, the average age was 70 years with a range of 56 to 101 years and 57 % of the participants were female. The most prevalent cardiovascular risk factor was history of smoking with 52% former smokers and 17 % current smokers. 1535 participants had a history of any depression, and 128 a history of stroke. 255 persons had AF at baseline, and another 311 developed AF during follow-up.

In our study population, a total of 699 incident depressive episodes occurred during 39,840 person-years. Of these episodes, 388 were depressive syndromes, including 99 DSM-defined major depressive disorders and dysthymias. Table 1 presents the risk of incident late-life depression related to AF. AF was not associated with depressive symptoms and syndromes combined. When adjusting for age and sex only, AF was related to depressive syndromes in the complete sample (HR 1.63; 95% CI 1.04-2.55), as well as the subsample of persons without a history of depression (HR 2.00; 95% CI 1.06-

Table 1 Atrial fibrillation (AF) and the risk of incident depression estimated with Cox' regression

	Depressive symptoms and depressive syndromes		Depressive syndromes only	
	HR (95%CI)	p-value	HR (95%CI)	p-value
Complete sample (n=4,750)				
AF, age and sex adjusted	1.21 (0.83-1.75)	.32	1.63 (1.04-2.55)	.03
AF, adjusted for all confounders*	1.18 (0.81-1.72)	.40	1.49 (0.94-2.37)	.09
Persons without history of depression (n=3,215)				
AF, age and sex adjusted	1.51 (0.92-2.49)	.11	2.00 (1.06-3.75)	.03
AF, adjusted for all confounders*	1.51 (0.90-2.54)	.12	1.60 (0.81-3.15)	.18

* adjusted for baseline age, sex, SES, ADL, history of depression, smoking, hypertension, history of ischemic cardiovascular disease, diabetes,
myocardial infarct, heart failure, stroke, transient ischemic attacks, use of antihypertensive medication

3.75). However, when all confounders were adjusted for, AF was not associated with these outcomes in either the complete sample or the subsample of persons without a history of depression. Moreover, in an additional time-varying analysis, that took changes in AF or confounder status after baseline into account, the risk estimates decreased even more: HR 1.18 (95% CI 0.88-1.57) for depressive symptoms and syndromes combined, and HR 1.25 (95% CI 0.85-1.83) for depressive symptoms only (complete sample).

Discussion

In this population-based cohort study, AF was not associated with an increased risk of incident depression anymore when all potential confounders were taken into account. A cross-sectional association between AF and depression has previously been established in four clinical populations.(1-4) Several prospective studies examined the risk of depression associated with (the cumulative burden of) a set of cardiovascular risk factors, including AF.(9-11) The results were, however, inconsistent for both any depression (9, 11), as well as DSM-defined depression.(9, 10) As these studies were not focused on AF, many potential confounders were not taken into account. To our knowledge, this is the first prospective study that specifically addressed the association between AF and incident depression.

The current study was based on a large cohort of community-dwelling elderly. Moreover, detailed information on the occurrence of AF and depression was collected continuously throughout the follow-up period. It is unlikely that information bias explains our results. If persons with cardiac disorders visited their GP or cardiologist more often, so that depressions were identified more easily, this would have led to an overestimation of the true risk. A potential source of selection bias might be that patients with cardiac disorders died before their depression was diagnosed, but this seems less likely as atrial fibrillation is mostly not an acute cause of mortality. We minimized confounding by adjusting for a substantial number of potential confounders. Some residual confounding may still have occurred, since we did not have baseline information on hyperthyroidism. Finally, we assessed whether lack of power could explain the results. However, the most parsimonious model, based on the criterium of 10% change in risk estimate, that included sex, age, history of depression and heart failure, did not yield materially different results.

We conclude that AF is not an independent risk factor for incident late-life depression.

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Chapter 5

Beta-blockers

Abstract

Objective. The aim of this study was to prospectively assess whether highly lipid-soluble, non-selective, or serotonergic receptor binding beta-blockers are associated with incident depression.

Methods. Between 1993 and 2005, 5,104 elderly persons were followed for incident depressions, identified by regular interview and continuous monitoring of medical records. Pharmacies provided online information on filled beta-blockers. We used multivariate Cox proportional hazard models to analyze the data.

Results. Overall, beta-blockers were not associated with depressive symptoms or syndromes. Highly lipid-soluble beta-blockers were associated with depressive symptoms during the first three months of use (HR 3.31; 95% CI 1.03-10.6). Non-selective beta-blockers conveyed an increased risk (HR 2.13; 95% CI 1.05-4.33), but only if also highly lipid-soluble (HR 3.45; 95% CI 1.08-11.0). Serotonergic receptor affinity was not significantly associated with depressive symptoms (HR 2.56; 95% CI 0.80-8.20). No group of beta-blockers was associated with incident depressive syndromes.

Conclusion. We conclude that lipophilic beta-blockers, mostly propranolol in our study, were associated with depressive symptoms.

Introduction

Soon after propranolol was marketed, physicians became concerned about depression in users of beta-adrenergic blockers. In 1967, a report indicated that 20 out of 89 patients receiving propranolol for cardiac arrhythmias developed depressive symptoms (1). Since then, numerous cases of depression in beta-blocker users were described in medical journals (2). These case reports were suggestive of a strong causal relationship between propranolol and depression (2).

The most widely proposed explanation for the relationship between beta-blockers and depression is that the drugs decrease noradrenergic activity in the brain.(3, 4) This suggests that non-selective beta-blockers, blocking beta-2 in addition to beta-1 adrenoceptors, may be more likely to induce depression than selective beta-blockers. Indeed, all beta-blockers that have ever been individually associated with an increased risk of depression are also non-selective: propranolol, oxprenolol, nadolol, sotalol and timolol (2, 5, 6). However, to our knowledge, this hypothesis has been investigated in only one study. This cross-sectional study yielded an odds ratio of 1.8 for DSM-defined major depression (95%CI: 1.1-3.1) for non-selective beta-blockers (7). Another hypothesis is that the affinity with serotonergic (5-HT1A) receptors forms the actual iatrogenic mechanism of action. Moreover, independent of the actual mechanism involved, lipophilic beta-blockers may be the most likely candidates for conveying an increased risk of depression because they pass the blood brain barrier most easily. Propranolol and oxprenolol, both lipophilic beta-blockers, have in fact been associated with an increased risk of depression (2, 6).

The objective of the current study was to examine the association between lipid-solubility, serotonergic receptor affinity, and non-selectiveness of beta-blockers and incident depression in a large cohort study among community-dwelling elderly. Participants were assessed prospectively and systematically for the occurrence of depressions.

Methods

Setting

The study was embedded in the Rotterdam Study, a prospective cohort study among 7,983 inhabitants of Ommoord, a district of Rotterdam, who were 55 or older at the start of the study in 1990. The Rotterdam Study focuses on the occurrence of common diseases in the elderly.(8) The Medical Ethics Committee of the Erasmus Medical Center Rotterdam approved the study and all participants provided written informed consent. Up till 2004, four examination rounds have taken place during which participants underwent an extensive interview and a physical examination. Continuous monitoring for major cardiovascular, neurological, and psychiatric diseases such as depression was achieved

through linkage with the medical files from general practitioners (GPs). Information on vital status was obtained from the municipal authorities.

Study population

The study population consisted of persons at risk for incident depression and was selected as follows. During the second examination round in the Rotterdam Study, the baseline of the current analysis, 5769 participants were screened for depressive symptoms. Participants filled out either the validated Dutch version of the Center for Epidemiologic Studies Depression Scale (CES-D) or the validated Dutch version of the Hospital Anxiety and Depression Scale (HADS)(9, 10). Persons with a score of 16 or higher on the CES-D or 9 or higher on the HADS were considered screen-positive. At baseline, we excluded 549 persons with depressive symptoms, 105 persons with dementia, 9 persons with bipolar disorder, and 2 persons lost to follow-up directly after screening. This resulted in a study population of 5104 persons free of depression at baseline.

Assessment of incident depression

Assessment of depression in the Rotterdam Study has been described in detail before (11). Information on the occurrence of incident depressions during follow-up was obtained from (1) psychiatric examinations, (2) self-reported histories of depression, and (3) medical records. The psychiatric examination during examination rounds consisted of a screening with the CES-D. Subsequently, a trained clinician conducted a semi-structured interview in screen-positive participants (Schedules for Clinical Assessment in Neuropsychiatry).(12) The self-reported history of depression, solicited during examination rounds, included standardized questions to ascertain whether and when participants had suffered from a depressive episode, and if so whether they had been treated. Trained research-assistants scrutinized the GPs' medical records and copied the information about a potential depression. Two research physicians and a psychologist independently assessed this information according to a predefined protocol, and discussed discordant assessments.

Based on these sources, we defined two categories of depressive episodes: (1) clinically relevant depressive symptoms, if at least one clinically relevant core symptom of major depression had been reported, and (2) depressive syndromes, which included depressive disorders that met DSM-IV criteria for major depression or dysthymia (13) and were diagnosed by a psychiatrist or another mental health professional, and other depressive syndromes that involved a depression recorded by a GP or other physician, self-reported depression for which the participant consulted a GP or a mental health professional, and DSM-IV minor depression. We defined the date-of-onset as the day of the first report of symptoms according to one of the sources described above, or the date of the first prescription of an antidepressant drug, whichever came first.

Exposure definition

The seven fully computerized pharmacies that serve the study area routinely store digitized information on all drugs dispensed to participants. More than 95 percent of the participants fill their prescriptions at one of these pharmacies. For each prescription, the ATC-code, prescribed daily dosage and number of tablets is registered. For each prescription, the duration was calculated by dividing the number of filled tablets by the prescribed daily number plus a carry-over period of seven days. We included all orally administered beta-blockers, as well as beta-blockers in combination-drugs. Participants were assigned the status of current user of a beta-blocker at the time a depression occurred, if the depression fell within the calculated prescription period. We distinguished two levels of lipid-solubility: low (atenolol, carteolol, practolol, nadolol, sotalol, timolol)/ moderate (acebutolol, bisoprolol, celiprolol, esmolol, labetalol, levobunolol, medroxalol, mepindolol, metoprolol, oxprenolol, pindolol), and high (alprenolol, betaxolol, bopindolol, bucindolol, bupranolol, carazolol, carvedilol, metipranolol, nebivolol, penbutolol, propranolol, talinolol, tertatolol). (14) The following beta-blockers were considered serotonergic antagonists: alprenolol, bopindolol, penbutolol, pindolol, and propranolol (15-17). Non-selective beta-blockers were: alprenolol, bucindolol, carteolol, carvedilol, labetalol, levobunolol, metipranolol, nadolol, oxprenolol, penbutolol, pindolol, propranolol, sotalol, and timolol.

Covariates

The following potential confounders were considered. We considered the socio-demographic variables age, sex, socio-economic status, and disability in activities of daily living in the analyses. Cardiovascular diseases were assessed as these are indications for beta-blocker use: hypertension, myocardial infarction, and heart failure. Finally, the following (relative) contraindications for beta-blocker use were accounted for: hypotension, chronic obstructive pulmonary disease, claudicatio intermittens, and a history of depression.

Socio-economic status was determined in terms of highest education attained and net income.(18) Disability in activities of daily living was assessed with the Modified Stanford Health Assessment Questionnaire.(19) Higher scores on this scale with a range of 1.0 to 4.0 represent more disability. Blood pressure was measured twice, after a minimum of 5 minutes rest, in sitting position at the right upper arm using a random zero sphygmomanometer. The average of the two measurements was used for our analysis. Hypertension was defined as diastolic blood pressure of 100 mmHg or above, or systolic blood pressure of 160 mmHg or above (20), or the use of antihypertensive drugs for the indication hypertension. Hypotension was defined as systolic blood pressure of 90 mmHg or below. Claudicatio intermittens was established with the Rose questionnaire during home-interviews.

A history of myocardial infarction was defined as self-reported myocardial infarction confirmed by information from medical records, or an ECG characteristic of prior

myocardial infarction according to the ICD-10 (code I21) as verified by a cardiologist (21). Heart failure was defined in accordance with the criteria of the European Society of Cardiology.(22) It required the presence of the typical signs or symptoms of heart failure, and confirmation of cardiac dysfunction on chest X-ray or echocardiography. Chronic obstructive pulmonary disease (COPD) was defined with an algorithm based on spirometry reports and information from medical files (23). The medical and pharmacy records also provided information on the date-of-onset of these events.

Statistical analysis

For the calculation of adjusted risk estimates with their 95% confidence intervals, we used Cox proportional hazards analyses with the outcomes 'depressive symptoms' and 'depressive syndromes', respectively. We defined the following exposures as time-dependent determinants of interest and compared them to no use: 1) use of any beta-blocker, 2) use of low/moderately and highly lipid-soluble beta-blockers, 3) use of serotonergic receptor non-binding and binding beta-blockers, and 4) use of selective and non-selective beta-blockers. We tested whether these exposures were associated with depression especially in the first three months of use, because in earlier reports depression began within a couple of weeks after starting treatment (2). Moreover, it is likely that patients who develop depression in the first months of treatment stop or switch to other drugs (potentially causing 'depletion of susceptibles'). We fitted a multivariate model for each outcome and exposure variable, adjusting for age, sex, and dosage expressed in terms of lower or higher than the Defined Daily Dose, which is the recommended dose for the main indication in an adult. Subsequently, we assessed whether the other confounders mentioned above changed the risk estimate by 1 percent or more. Only history of depression, and the time-varying variables myocardial infarction, heart failure, and chronic obstructive pulmonary disease changed the point estimate and these variables were included in the multivariate models.

In the analyses, each participant contributed person-years until follow-up ended either with an episode of depressive symptoms or a depressive syndrome, dementia, death, loss-to-follow-up, or the end of study on October 1, 2005, whichever came first. For all statistical analyses we used SPSS for Windows, version 15.0.

Results

We identified 736 new-onset depressive episodes in 42,145 person-years, of which 329 were episodes of depressive symptoms, and 407 depressive syndromes. Table 1 presents the baseline characteristics of the study sample. The average age was 70 years with a range of 56 to 101 years and 58 % of the participants were female. The most prevalent cardiovascular risk factor was smoking (49% former smoker, 18 % current smoker).

Table 1 Baseline characteristics of the study population (N=5,104)

Characteristic	Descriptive
Age, mean (SD)	70.0 (8.3)
Female sex, no (%)	2941 (57.7)
Education, primary school only, no (%)	936 (18.6)
Income, median (range)	2749 (750-7000)
Disability, mean (range)	1.31 (1.00-4.00)
History of depression, no (%)	1643 (32.2)
Smoking,	
- former smoker, no (%)	2420 (48.6)
- current smoker, no (%)	931 (18.3)
Diastolic blood pressure, mean (range)	77 (40-128)
Systolic blood pressure, mean (range)	141 (70-242)
Myocardial infarction, no (%)	563 (11.0)
Chronic heart failure, no (%)	206 (4.0)
Chronic obstructive pulmonary disease, no (%)	175 (3.4)

During the study period, 39 % of the study population filled at least one prescription for a beta-blocker. More than two third of filled prescriptions for beta-blockers consisted of atenolol and metroprolol (see table 2). Propranolol was the most frequently prescribed highly lipid-soluble and serotonergic receptor binding beta-blocker. Table 2 shows that lipid-solubility and serotonergic receptor affinity are highly correlated.

Table 2 Characteristics of the beta-blockers used during the study period*

Generic name	Lipid-solubility	Serotonergic affinity	Non-selectivity	Percentage
Atenolol	L	N	N	37%
Metoprolol	M	N	N	32%
Bisoprolol	M	N	N	12%
Sotalol	L	N	Y	11%
Propranolol	H	Y	Y	3%
Pindolol	M	Y	Y	1%
Labetolol	M	N	Y	1%
Penbutolol	H	N	Y	<1%
Nebivolol	M	N	N	<1%
Celiprolol	M	N	N	<1%
Oxprenolol	M	N	Y	<1%
Timolol	L	N	Y	<1%
Acetobutolol	M	N	N	<1%
Alprenolol	H	Y	Y	<1%
Bevantolol	M	N	N	<1%

* L stands for low, M for intermediate, H for high, N for no and Y for Yes

Table 3 shows the results of the multivariate Cox proportional hazard analyses. Overall, use of a beta-blocker was not associated with depressive symptoms or syndromes, either in the first 90 days of use or afterwards. Highly lipid-soluble beta-blockers were associated

with depressive symptoms in the first 90 days of use (HR 3.31; 95% CI 1.03-10.6), as were non-selective beta-blockers (HR 2.13; 95% CI 1.05-4.33). Serotonergic binding also conveyed an increased, albeit non-significant, risk of depressive symptoms in the first 90 days of use (HR 2.56; 95% CI 0.80-8.20). There were no associations when these groups of beta-blockers were used longer than three months. Nor was there a relation between these groups of beta-blockers and depressive syndromes.

Table 3 Beta-blocker use and the risk of incident depression using multivariate Cox' regression (n=5104)*

Exposure	Depressive symptoms				Depressive syndromes			
					HR (95%CI)	p-value		
	Age and sex adjusted		Fully adjusted		Age and sex adjusted		Fully adjusted	
	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
All beta-blocker:								
No use (ref)	-		-		-		-	
Use during 1-90 days	0.78 (0.38-1.62)	.502	0.76 (0.37-1.59)	.469	1.02 (0.54-1.91)	.957	0.99 (0.53-1.84)	.967
Use during > 90 days	0.85 (0.44-1.63)	.623	0.87 (0.45-1.66)	.661	0.79 (0.44-1.40)	.415	0.80 (0.45-1.43)	.455
Highly lipophilic beta-blocker:								
no use (ref)	-		-		-		-	
use during 1-90 days	3.60 (1.13-11.5)	.031	3.31 (1.03-10.6)	.044	1.96 (0.48-8.00)	.347	1.77 (0.43-7.23)	.429
use during > 90 day	1.51 (0.37-6.17)	.568	1.47 (0.36-6.02)	.592	-**		-**	
Serotonergic binding beta-blocker:								
no use (ref)	-		-		-		-	
use during 1-90 days	2.93 (0.92-9.36)	.069	2.56 (0.80-8.20)	.112	1.65 (0.40-6.72)	.487	1.42 (0.35-5.79)	.628
use during > 90 day	1.67 (0.52-5.32)	.388	1.58 (0.50-5.06)	.437	0.47 (0.07-3.36)	.450	0.43 (0.06-3.12)	.407
Non-selective beta-blocker:	-		-		-		-	
no use (ref)	2.25 (1.11-4.56)	.025	2.13 (1.05-4.33)	.036	1.51 (0.69-3.29)	.304	1.38 (0.36-3.01)	.423
use during 1-90 days	0.76 (0.31-1.91)	.564	0.75 (0.30-1.88)	.543	0.91 (0.42-1.99)	.811	0.89 (0.41-1.94)	.766
use during > 90 day								

* All models are adjusted for treatment dosage (<= 1 DDD versus > 1 DDD). The fully adjusted models also included age, sex, history of depression, myocardial infarction, heart failure, and chronic obstructive pulmonary disease.

** The model could not be fitted due to too few observations.

Due to collinearity between lipid-solubility and serotonergic receptor affinity, we could not fit one statistical model with all three groups of beta-blockers in order to test whether one group in particular accounted for the increase in the risk of depressive symptoms. However, non-selective, highly lipid-soluble beta-blockers carried a risk of depressive symptoms in the first 90 days of use (HR 3.45; 95% CI 1.08-11.0) similar that of all highly lipid-soluble beta-blockers (HR 3.31; 95% CI 1.03-10.6). Non-selective beta-blockers with low to moderate lipid-solubility were not associated with an increased risk of depressive symptoms in the first 90 days of use (HR 1.70; 95% CI 0.73-3.96). When we restricted exposure further to highly lipid-soluble, non-selective beta-blockers with serotonergic affinity, that is propranolol and alprenolol, the risk of depressive symptoms in the first 90 days of use was 3.81 (95% CI 1.19-12.2).

Discussion

In this prospective study, we found that highly lipid-soluble beta-blockers were associated with a more than threefold increased risk of incident depressive symptoms in the first three month of use. The risk was particularly high for highly lipid-soluble beta-blockers that also bind to serotonergic receptors. Non-selective beta-blockers were only associated with an increased risk of depressive symptoms if they were also highly lipid-soluble. Beta-blockers in general were not associated with an increased risk of depressive symptoms or syndromes.

The association between depression and beta-blockers is controversial. With respect to beta-blockers in general, a prospective population-based study reported a risk of 2.6 for anti-depressant use (6), but this result has not been replicated since in prospective observational studies (24-26), or in a meta-analysis of randomized studies (27). The results of our study are in line with the null findings of the latter studies. With respect to highly lipid-soluble beta-blockers in particular, a review of 24 published case reports suggested a likely causal relationship between propranolol and depression.(2) Nine reports met the Naranjo criteria for causality (28). In all nine case described, depression began within a couple of weeks after treatment had started. Moreover, in a large Canadian cohort study, the risk of antidepressant use within 12 months after the start of propranolol was 4.8 times that of non-users and 2.1 times that of other study drug users (6). Three quarters of the depressions had occurred within the first half year of treatment. When patients are closely followed for the effect of stopping and restarting the use of a drug, as is common for a case report, an effect will probably be noted sooner. Another cohort study found a significantly increased standardized mortality ratio due to suicide of 2.7 in users of beta-blockers with high lipid-solubility, but not with low or medium lipid-solubility.(29) The results of our study also confirm the hypothesis that lipophilic beta-blockers cause more depression than do hydrophilic beta-blockers. Lipophilic beta-blockers more readily pass the blood-brain-barrier. However, previous prospective studies did not show an association between propranolol and depressive symptoms (25, 26). Insufficient power may have contributed to these results. In one cohort study, antidepressant drug use served as an indicator of depression(26), but in later studies, this indicator has been shown to represent a depression in only 43-56% of users (30-33). Medical records were used to verify the diagnosis of depression in antidepressant users in the other cohort study, but this yielded only 28 cases. (25) No association was found either with lipid-solubility or propranolol in particular in meta-analyses of controlled clinical trials (2, 27), but trials often lack systematic and timely assessment of depression (2, 3, 29).

Lipid-solubility is not a pathophysiological mechanism of action in itself, but rather a prerequisite for the depressogenic effect of beta-blockers. Therefore, we also studied whether a serotonergic (5-HT1A) or beta-2 adrenergic receptor antagonism that some beta-blockers exert could be involved. Overall, beta-blockers with serotonergic receptor af-

finity were not significantly associated with incident depression in our study. On the other hand, non-selective (beta-2 blocking) beta-blockers were associated with an increased risk of incident depression. An odds ratio of 1.8 for DSM-defined major depression (95%CI: 1.1-3.1) has been found before in a cross-sectional study (7). In animal research, the beta-1 and beta-2 adrenoceptor antagonists alprenolol, pindolol, propranolol, and sotalol were found to block the action of nortriptyline, as shown by Yalcin et al in a study in mice (34). Conversely, salbutamol, a beta-2 adrenergic stimulant had been found to be as effective as clomipramine in a small trial with depressed inpatients (35). Positive correlations were also observed between the number of lymphocyte beta-adrenoceptors and the rating on the Beck and Hamilton depression questionnaires in patients with major depressive disorder (36). Yet, we also found that non-selective beta-blockers with high lipid-solubility, i.e. propranolol, penbutolol and alprenolol in our study population (see table 2), have a similar risk of depressive symptoms as the whole group of highly lipid-soluble beta-blockers. This suggests that the increased risk that we found for non-selective beta-blockers may be explained by the fact that many of these beta-blockers are highly lipid-soluble. Moreover, non-selective beta-blockers with low to moderate lipid-solubility were not related to depression in our study. When we studied highly lipid-soluble beta-blockers with serotonergic affinity, in our study consisting of alprenolol and in most users propranolol, the risk was similar to that of the whole group of highly lipid-soluble beta-blockers as well. Given the abundance of studies that have implicated a depressogenic effect of propranolol, it is possible that propranolol itself explains our findings.

It has been suggested that drug-induced depressions present with a different phenomenology (37). For instance, medication may cause depressive symptoms instead of depressions that meet DSM criteria. Our findings are compatible with this suggestion. We found an increased risk for episodes of depressive symptoms in the first three months of use, but not for depressive syndromes. Given that prescription and treatment protocols that were in use during the study period required physicians to evaluate the effect of a drug within three months, it is likely that adverse effects such as depressive symptoms are identified within this period.

Strengths of our study are the large study population, long follow-up time, and systematic psychiatric work-up. Incident depressions were identified from multiple sources, among which medical records. Moreover, our findings apply to the heterogeneous sample of ambulatory elderly patients that, in our view, are typical of today's beta-blocker users. A limitation of our study is that some information bias might have occurred. It is conceivable that treating physicians are alert to the adverse effect of depression in users of beta-blockers, especially propranolol (25). However, we did not find that people with a history of depression received propranolol less or more often than people without such a history. Finally, it cannot be ruled out that in some instances propranolol was prescribed for conditions that are risk factors for depression such as anxiety, migraine, alcoholism and thyroid disease.

We conclude that the use of high lipid-soluble beta-blockers, possibly propranolol in particular, may give rise to depressive symptoms in late life, and that this adverse effect is usually detected in the first months of treatment. As depressive symptoms and beta-blocker use are both very common in the elderly, physicians should be alert to this adverse effect.

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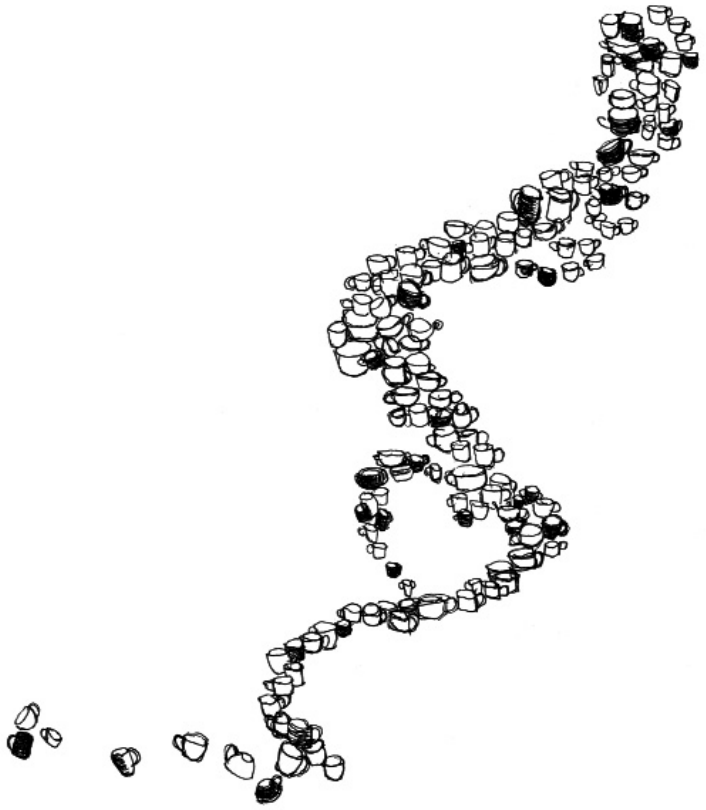
Part III

Vascular brain disease and late-life depression

Chapter 6

Cerebrovascular risk factors



Abstract

Introduction. The 'vascular depression' hypothesis suggests that late-life depression results from vascular brain damage. We studied the longitudinal association between cerebrovascular risk factors and incident depression in a large population-based study.

Methods. 2,931 persons aged 61 or older were followed. Data on a comprehensive set of cerebrovascular risk factors was collected at baseline. Participants received a psychiatric assessment five years later to establish DSM-IV diagnoses.

Results. Only current smoking and anti-hypertensive drug use were independently associated with incident depressive symptoms. Diabetes mellitus, and the Framingham stroke risk score were related to incident depressive disorder. No relation with depression was observed for cholesterol, diastolic and systolic blood pressure, history of cardiovascular disease, atrial fibrillation, left ventricular hypertrophy, or the use of statins and anticoagulants.

Conclusion. These results moderately support the 'vascular depression' hypothesis.

Introduction

According to the vascular depression hypothesis, cerebrovascular disease may predispose, precipitate or perpetuate late-life depression (1, 2). Atherosclerotic lesions to brain circuits responsible for affective regulation are assumed to form the central mechanism (3). Such damage might also affect treatment success and the course of illness.

When comparing depressed geriatric patients with controls, neuroimaging and autopsy studies showed that lesions in frontal deep white matter, basal ganglia and gray matter, as well as atrophy were more prevalent (4). One prospective study showed that lesions on magnetic resonance imaging were also associated with incident depression (5). To further test the vascular depression hypothesis, the longitudinal association between risk factors of vascular brain damage and late-life depression can be examined. The following cerebrovascular risk factors (CVRFs) have been established: smoking, hypertension, dyslipidemia, diabetes mellitus, history of cardiovascular disease, and atrial fibrillation (4, 6-12).

To date only two population-based cohort studies have studied this relationship. They present conflicting results. In a Korean population, after two years of follow-up, low and high total cholesterol, low HDL cholesterol and a history of heart disease were associated with incident depression (GMS), but hypertension and diabetes were not (13). In an American study, none of the risk factors included was associated with depressive symptoms (CES-D) after one year of follow-up (14). Both studies relied on self-reported vascular disease and had a relatively short follow-up period. Furthermore, the potential bias introduced by the use of cardiovascular medication has received little attention. They are the most widely prescribed drugs in the elderly (15) and have been associated with depression as well (16, 17).

The purpose of this study was to examine whether CVRFs at baseline were associated with incident depressive symptoms and depressive disorders in the general elderly population. CVRFs were systematically assessed and the follow-up period covered more than five years.

Methods

Setting

This investigation was embedded in the Rotterdam Study, a prospective study in a cohort of community-dwelling elderly residing in Ommoord, a district of Rotterdam. The Rotterdam Study focuses on the determinants of vascular, neuro-degenerative, ophthalmologic, locomotor and psychiatric diseases in the elderly (18). The Medical Ethics Committee of the Erasmus Medical Center Rotterdam approved the study, and written informed consent was obtained from all participants.

The third examination round, which took place from March 1997 to December 1999, served as the baseline for the current study. The participants were 61 years or older at that time. Trained interviewers administered an extensive questionnaire covering current health status, health related behavior, medication use, medical history and socio-economic background. As part of the home interview, a cabinet check of actual medication use was carried out. During the visit to the study center, laboratory assessments and clinical examinations were performed. In the third round an assessment of depressive disorders was added to the study protocol (see below). The occurrence of incident depressive symptoms and depressive disorders was assessed again at follow-up, i.e. during the fourth round, which was conducted between January 2002 and October 2004.

In order to complement the data retrieved from the examination rounds, from the start of the Rotterdam Study all participants were continuously monitored for the occurrence of disease. Automated linkage with files from general practitioners provided information on clinical diseases such as myocardial infarction, atrial fibrillation, and diabetes mellitus. Two research physicians independently classified all information. If they could not reach consensus, the judgment of a specialist was considered decisive.

Study population

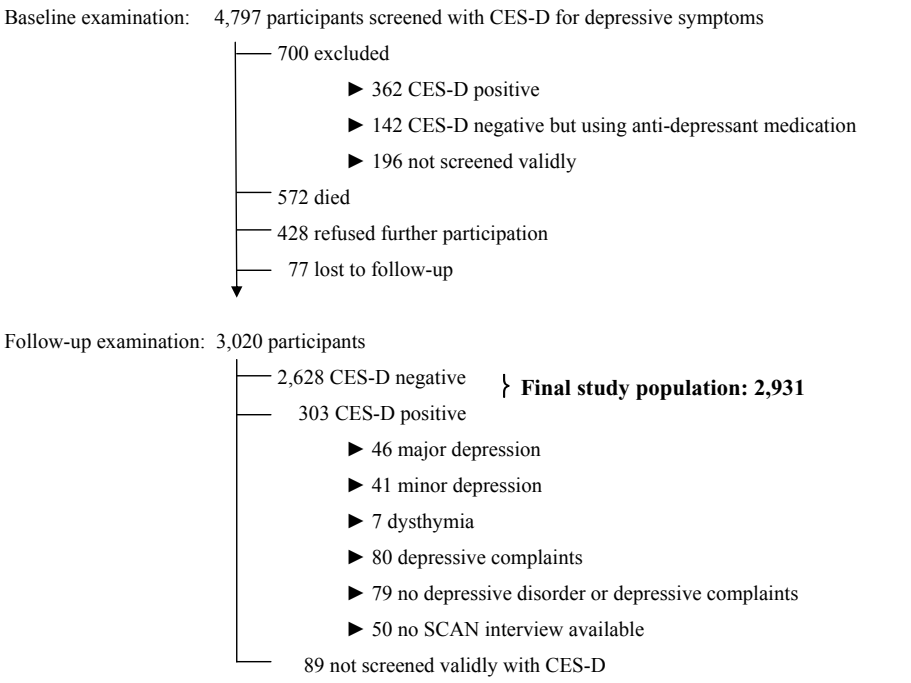
Of 5,990 invited participants, 4,797 people took part in the baseline examination (80%). We excluded 362 participants with depressive symptoms and 196 participants who did not answer enough items of the depression screening instrument to calculate a valid score (see figure 1). As the use of anti-depressive medication within six months before the interview might have influenced the number and severity of reported depressive symptoms, we also excluded the 142 participants who did not report depressive symptoms but used an antidepressant at baseline. After the baseline examination, 572 individuals died, so that 3,525 participants could be invited for the follow-up examination. 3,020 of them took part (86%). Eventually, 2,931 participants provided valid data about depressive symptoms at follow-up and comprise the study sample for the current analysis.

Assessment of depressive symptoms and depressive disorders

During the baseline and follow-up examination round, we used the same two-step procedure to assess depressive symptoms and depressive disorders. First, the participants were screened for depressive symptoms during the home-interview with a Dutch, validated version of the Center for Epidemiologic Studies Depression Scale (CES-D) (19). This questionnaire contains 20 questions with possible scores of 0 to 3. Participants with scores of 16 or higher were considered screen-positive. This cut-off represents clinically significant depressive symptoms.

Next, the screen-positive participants were invited for a clinical interview. A trained psychiatrist, geriatrician or psychologist conducted the psychiatric work-up using the Dutch

Figure 1: flow diagram of study population



version of the Present State Examination, a semi-structured psychiatric interview included in the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (20). Major and minor depressive disorders as well as dysthymia were classified according to the DSM-IV criteria, with an algorithm based on the item-scores.

As explicated above, our study population consisted of participants who were free of depressive symptoms (CES-D <16) at baseline and were at risk of incident depressive symptoms (CES-D >= 16) or an incident DSM-IV defined depressive disorder.

Assessment of cerebrovascular risk factors (CVRFs)

We studied the following CVRFs: smoking, diastolic and systolic blood pressure, diabetes mellitus, total and HDL-cholesterol, history of cardiovascular disease, atrial fibrillation, and left ventricular hypertrophy on ECG.

Self-reported smoking was categorized into never, former, and current. Blood pressure was measured twice, after a minimum of five minutes rest, in sitting position at the right upper arm using a random zero sphygmomanometer. The average of the two measurements was calculated. The criteria for diabetes mellitus were: fasting plasma glucose level of 7.0 mmol/l or over, non-fasting glucose or an oral glucose tolerance test of 11.1 mmol/L or

over, or treatment with an antidiabetic medication or diet. Total serum cholesterol and HDL-cholesterol were determined with an automated enzymatic procedure.

Angina pectoris and claudicatio intermittens were established with the Rose questionnaire. Other 'signs' of coronary insufficiency were a history of coronary artery bypass grafting, and percutaneous transluminal coronary angioplasty. History of myocardial infarction was defined as self-reported myocardial infarction confirmed by a physician, or myocardial infarction on the echocardiography (ECG) made during the centre visit. A diagnosis of heart failure was classified as definite, probable, possible, or unlikely in accordance with the criteria of the European Society of Cardiology (21), and we included only definite and probable cases included in the analysis.

For the diagnosis of atrial fibrillation or atrial flutter, an ECG that verified the diagnosis was required. The ECGs that were recorded at the research centre were analyzed with the Modular ECG Analysis System (22). The ECGs were also used to assess the presence of left ventricular hypertrophy. Cases with left ventricular hypertrophy were defined as having a left ventricular mass index ≥ 104 g/m2 in women and 116 g/m2 in men.

Information on medication use was derived from the seven fully computerized pharmacies that serve the neighborhood. Ninety percent of the participants of the Rotterdam Study fill their prescriptions at one of these pharmacies. With regard to the use of antihypertensive medication, statins, coumarines or salicylates, we assumed that a participant was a current user when the data from the home interviews or pharmacies showed that (s)he had filled a prescription for either of these drugs within three months before the date of the home-interview of the third round. The following antihypertensive drugs were included: diuretics, beta-blockers, ace-inhibitors, calcium channel blockers, and a miscellaneous group including reserpine. We also checked whether participants used antidepressants (tricyclic antidepressants, (non)selective serotonin reuptake inhibitors, or other) within six months before the baseline and follow-up examination, because this might have influenced the number and severity of reported depressive symptoms.

On the basis of the abovementioned information we computed the 10-year Framingham stroke risk score. This composite score was developed to identify persons at substantially increased stroke risk, resulting from their vascular risk profile (12). It encompasses age, systolic blood pressure, antihypertensive treatment, history of cardiovascular disease (including myocardial infarction, angina pectoris, coronary insufficiency, claudicatio intermittens, and chronic heart failure), diabetes mellitus, smoking, atrial fibrillation and left ventricular hypertrophy. Different weights are attributed to these risk factors for men and women. Men can be assigned up to 30 and women up to 27 points, corresponding with 10-year probabilities of stroke of 87.9% and 84.4% respectively.

Assessment of confounders

Age, sex, socio-economic status, disability in activities of daily living, cognitive function and body mass index were assumed to confound the association between CVRFs and both depressive symptoms and depressive disorders (23, 24). We adjusted for highest education attained as well as net income per month in order to adjust as fully as possible for the effect of socio-economic status (25). Disability in activities of daily living was assessed with the Modified Stanford Health Assessment Questionnaire (26), and cognitive status with the Mini Mental State Examination (27). Height and weight were measured with the participant in light underclothing and the body mass index (kg/m2) was calculated.

Data analysis

We examined the longitudinal relationship between CVRFs and incident depressive symptoms with linear regression. These symptoms were measured with the CES-D on a continuous scale from 0 to 60. First, we determined the association between the individual CVRFs at baseline and depressive symptoms at follow-up adjusted for age and sex. Although blood pressure was measured continuously, we used quintiles of diastolic and systolic blood pressure in the models of this risk factor in order to facilitate the interpretation of the results. When blood pressure was added as a confounder in the multivariate models of the other risk factors, we corrected for blood pressure levels using the continuous measure in order to enhance the precision of the correction. We also analyzed with an F-test the effect of adding the quadratic terms of diastolic blood pressure and total cholesterol to these models, because other studies have found u-shaped relationships between these variables and cerebrovascular disease or depression (11, 13). The regression models were adjusted for antidepressant use at follow-up, but this did not change the coefficients materially.

We used logistic regression to analyze the association between the individual CVRFs and the depressive disorders diagnosed in the clinical interviews. Participants with a major or minor depression or dysthymia were considered incident cases. Persons with some depressive complaints but not enough to fulfill the criteria of minor or major depression or dysthymia were restricted from this analysis. Again, we started with analyzing the association between the individual CVRFs and the depressive syndromes adjusting for age and sex, and subsequently analyzed with a likelihood ratio-test the effect of adding the quadratic terms of diastolic blood pressure and total cholesterol to these models.

Finally, for both outcomes, multivariable models were fitted, in which all risk factors, including the quadratic terms of diastolic blood pressure, and the presumed confounders were included. For the Framingham stroke risk score, a separate multivariable model was fitted, because this score encompasses almost all other individual risk factors. The variables education and (log-transformed) income were entered as continuous variables in the multivariable models. None of the abovementioned models was adjusted for baseline CES-D

in order to avoid bias as a result of regression to the mean in CES-D scores. Nor did we adjust for history of depression, as this would eliminate any possible effect of CVRFs on depression in the years prior to baseline.

Two-sided p-values of <0.05 were considered statistically significant. For all statistical analyses we used SPSS for Windows, version 13.0.

Results

After a follow-up of on average five years, there were 303 persons with a positive CES-D score among the 2,931 participants who formed the study population for the analyses relating to depressive symptoms (see flow diagram). 253 of the 303 screen-positive persons received a psychiatric work-up. There were 94 subjects with an incident depressive disorder: 46 persons fulfilled the DSM-IV-criteria for a major depression, 41 those for a minor depression, and 7 those for dysthymia. In 80 participants, no diagnosis of a depressive disorder according to DSM criteria was made using the psychiatric interview due to insufficiently severe depressive symptoms. These 80 persons with 'depressive complaints' and another 50 with no psychiatric work-up were excluded. The analyses relating to depressive disorders were based on the remaining 2,801 participants.

Table 1 presents the baseline characteristics of the study sample. The average age was 71 years with a range of 61 to 95 years and 58% of the participants was female. The most prevalent cerebrovascular risk factor was smoking (51% former smoker, 15.6% current smoker). The average 10-year Framingham stroke risk score was 12 in both men and women, which is equivalent to a 10-year probability of stroke of 12.9% and 9.2%, respectively.

Table 2 shows the results for the association between CVRFs at baseline and incident depressive symptoms after five years of follow-up. Increasing age (beta=0.16; 95% CI=0.12-0.20), female sex (beta=1.60; 95% CI=1.12-2.09), current smoking (beta=1.53; 95% CI=0.79-2.28), a history of cardiovascular disease (beta=0.96; 95% CI=0.33-1.59), the use of antihypertensives (beta=1.14; 95% CI=0.65-1.64), and the use of anticoagulants (beta=0.73; 95% CI=0.12-1.34) were statistically significantly associated with reporting depressive symptoms at follow-up. The 10-year Framingham stroke risk score was also associated with the occurrence of incident depressive symptoms (beta=0.14; 95% CI=0.07-0.20). In the multivariate model, only increasing age (beta=0.10; 95% CI=0.05-0.15), female sex (beta=1.43; 95% CI=0.75-2.11), current smoking (beta=1.68; 95% CI=0.83-2.53), and use of anti-hypertensives (beta=1.04; 95% CI=0.42-1.65) remained significantly associated with incident depressive symptoms at follow-up.

In a post-hoc analysis of smoking, we examined the association between pack-years and depressive symptoms in current and former smokers. We found a statistically significant

Table 1 Baseline characteristics of the study population (N=2,931)

Characteristic	Descriptives
Age, mean (SD)	71.0 (6.3)
Female sex, no (%)	1699 (58.0)
Education, primary school only, no (%)	419 (14.5)
Income, median (range)	2550 (750-7000)
Disability, mean (range)	0.4 (0.0-2.8)
MMSE, mean (SD)	27.9 (1.65)
BMI, mean (SD)	26.9 (3.9)
Cerebrovascular risk factors	
Smoking,	
former smoker, no (%)	1496 (51.0)
current smoker, no (%)	457 (15.6)
Diastolic blood pressure, mean (SD)	76 (11.0)
Systolic blood pressure, mean (SD)	143 (20.8)
Diabetes mellitus, no (%)	391 (13.4)
Total cholesterol, mean (SD)	5.8 (1.0)
HDL-cholesterol, mean (SD)	1.4 (0.4)
Cardiovascular disease, no (%)	522 (17.8)
Atrial fibrillation, no (%)	139 (4.9)
Left ventricular hypertrophy on ECG, no (%)	71 (2.5)
Medication	
Anti-hypertensive treatment, no (%)	1147 (39.1)
Statines, no (%)	330 (11.3)
Anti-coagulant use, no (%)	576 (19.7)
Framingham stroke risk score, mean (SD)	12 (4.8)

association between packyears and depressive symptoms only in former smokers (beta = 0.023; 95% CI= 0.01-0.04; p=0.004), but no significant association in current smokers (beta =0.027; 95% CI= -0.12-0.07; p=0.17) in the multivariable analyses.

Table 3 shows the results for incident DSM-defined depressive disorders at five year follow-up. Besides increasing age (OR=1.05; 95% CI=1.02-1.08) and female sex (OR=2.40; 95% CI=1.47-3.89), the 10-year Framingham stroke risk score was the only variable that was associated with the occurrence of depressive disorders (OR=1.06; 95% CI=1.00-1.11). In the multivariable model, however, apart from female sex (OR=2.40; 95% CI=1.21-4.76), diabetes (OR=2.07; 95% CI=1.11-3.85) increased the risk of depressive disorders.

To assess the potential effect of excluding the 50 participants who did not agree to a psychiatric interview, we performed an additional analysis in which we included the 50 participants in the logistic regression as if they had a depressive disorder. In the models for individual risk factors, the point estimates for sex, diabetes, atrial fibrillation and anti-hypertensive medication were attenuated by more than 10%. In the multivariable model, the point estimates for sex, former smoking, current smoking, and diabetes were attenuated.

Table 2 The association between cerebrovascular risk factors and incident depressive symptoms estimated with linear regression (N=2,931)

Variables	Models for individual risk factors*			Multivariable model#		
	Beta	95% CI	p-value	Beta	95% CI	p-value
Age, in yrs	0.20	0.17 – 0.25	.000	0.11	0.06 – 0.16	.000
Female sex	2.27	1.76 – 2.77	.000	1.73	1.03 – 2.43	.000
Cerebrovascular risk factors						
Smoking,						
- former smoker	0.10	-0.51 – 0.71	.741	0.07	-0.59 – 0.74	.832
- current smoker	1.74	0.95 – 2.52	.000	1.92	1.04 – 2.80	.000
Diastolic blood pressure, mmHg						
- quintile 1: 42 - 66	0.17	-0.64 – 1.00	.68	0.06	-0.86 – 0.98	.901
- quintile 2: 67 - 72	-.49	-1.30 – 0.32	.23	-0.73	-1.60 – 0.14	.101
- quintile 3: 73 - 77 (reference group)	0.00	-	-	0.00	-	-
- quintile 4: 78 - 84	-.44	-1.26 – 0.38	.30	-0.34	-1.23 – 0.55	.456
- quintile 5: 85 - 146	0.03	-0.78 – 0.84	.94	-0.08	-1.01 – 0.85	.870
Systolic blood pressure, mmHg						
- quintile 1: 87 - 125 (reference group)	0.00	-	-	0.00	-	-
- quintile 2: 126 - 136	-0.11	-0.91 – 0.70	.794	-0.25	-1.14 – 0.64	.583
- quintile 3: 137 - 146	-0.27	-1.09 – 0.55	.517	-0.31	-1.25 – 0.64	.527
- quintile 4: 147 - 159	-0.29	-1.10 – 0.51	.477	-0.33	-1.31 – 0.65	.506
- quintile 5: 160 - 236	-0.34	-1.15 – 0.47	.412	-0.48	-1.52 – 0.57	.372
Diabetes mellitus	0.76	0.02 – 1.50	.043	0.73	-0.10 – 1.57	.085
Total cholesterol	-0.03	-0.35 – 0.21	.609	0.01	-0.31 – 0.30	.981
HDL-cholesterol	-0.52	-1.21 – 0.16	.134	0.39	-0.39 – 1.17	.326
Cardiovascular disease	1.17	0.50 – 1.84	.001	0.28	-0.51 – 1.07	.486
Atrial fibrillation	0.66	-0.53 – 1.84	.278	-0.19	-1.50 – 1.12	.774
Left ventricular hypertrophy on ECG	0.08	-1.63 – 1.62	.992	-0.60	-2.36 – 1.17	.508
Medication						
Anti-hypertensives	1.23	0.71 – 1.75	.000	1.10	0.46 – 1.74	.001
Statines	0.58	-0.21 – 1.36	.153	0.20	-0.72 – 1.12	.674
Anti-coagulants	0.83	0.19 – 1.48	.011	0.33	-0.45 – 1.10	.406
Framingham stroke risk score	0.16	0.09 – 0.23	.000	0.06	-0.04 – 0.15	.261$

* Adjusted for age and gender; # adjusted for age, sex, education, income, disability, cognitive function, BMI, all other CVRFs and medication; $ adjusted for age, sex, education, income, disability, cognitive function, BMI.

Discussion

This prospective study showed that besides smoking and the use of antihypertensive medication no vascular risk factor was independently associated with the occurrence of incident depressive symptoms in a cohort of community-dwelling elderly. Diabetes mellitus and the Framingham stroke risk score were the only variables that were independently associated with the occurrence of a major or minor depressive disorder.

Table 3 The association between cerebrovascular risk factors and incident depressive disorders estimated with logistic regression (N=2,801)

Variables	Models for individual risk factors*			Multivariable model#		
	OR	95% CI	p-value	OR	95% CI	p-value
Age, in yrs	1.05	1.02 – 1.08	.002	1.03	0.98 – 1.07	.289
Female sex	2.40	1.47 – 3.89	.000	2.40	1.21 – 4.76	.012
Cerebrovascular risk factors						
Smoking,						
- former smoker	1.18	0.72 – 1.92	.512	1.22	0.70 – 2.24	.445
- current smoker	1.57	0.85 – 2.90	.149	1.89	0.91 – 3.92	.087
Diastolic blood pressure, mmHg						
- quintile 1: 42 - 66	1.05	0.57 – 1.93	.882	1.06	0.51 – 2.20	.886
- quintile 2: 67 - 72	0.79	0.41 – 1.52	.474	0.66	0.29 – 1.49	.315
- quintile 3: 73 - 77 (reference group)	1.00	-	-	1.00	-	-
- quintile 4: 78 - 84	0.65	0.32 – 1.33	.240	0.82	0.37 – 1.82	.631
- quintile 5: 85 - 146	1.21	0.65 – 2.24	.543	1.36	0.63 – 2.93	.434
Systolic blood pressure, mmHg						
- quintile 1: 87 - 125 (reference group)	1.00	-	-	1.00	-	-
- quintile 2: 126 - 136	0.90	0.46 – 1.73	.742	1.00	0.46 – 2.14	.993
- quintile 3: 137 - 146	0.86	0.44 – 1.68	.652	0.74	0.31 – 1.75	.488
- quintile 4: 147 - 159	0.95	0.50 – 1.81	.882	0.97	0.42 – 2.22	.936
- quintile 5: 160 - 236	0.75	0.38 – 1.48	.409	0.68	0.28 – 1.70	.414
Diabetes mellitus	1.31	0.75 – 2.29	.340	2.07	1.11 – 3.85	.022
Total cholesterol	0.89	0.70 – 1.13	.327	1.00	0.76 – 1.32	.992
HDL-cholesterol	0.69	0.38 – 1.27	.238	1.02	0.52 – 2.02	.947
Cardiovascular disease	1.54	0.93 – 2.55	.094	0.92	0.46 – 1.84	.816
Atrial fibrillation	2.09	1.01 – 4.31	.048	2.03	0.88 – 4.66	.096
Left ventricular hypertrophy on ECG	2.31	0.89 – 5.99	.085	1.19	0.33 – 4.30	.791
Medication						
Anti-hypertensives	1.51	0.99 – 2.31	.054	1.57	0.89 – 2.75	.117
Statines	1.28	0.69 – 2.38	.441	1.51	0.73 – 3.15	.271
Anti-coagulants	1.15	0.70 – 2.92	.597	0.92	0.47 – 1.78	.801
Framingham stroke risk score	1.06	1.00 – 1.11	.039	1.07	1.00 – 1.14	.021$

* Adjusted for age and gender; # adjusted for age, sex, education, income, disability, cognitive function, BMI, all other CVRFs and medication; $ adjusted for age, sex, education, income, disability, cognitive function, BMI.

The positive association that we found between current smoking and depressive symptoms is in line with results of many cross-sectional (28, 29) and prospective studies (30, 31). If a relationship exists between smoking and depression through vascular damage, as suggested by the vascular depression hypothesis, one would expect to find an association in current as well as former smokers. As endothelial function may improve after stopping smoking, it is likely that the risk in former smokers is lower. When testing the 'dose-response' relationship between packyears and depressive symptoms in former and current smokers, we found a statistically significant association for the former smokers only. It seems that, although strong, the link between smoking and major depression is not very

straightforward (32). First, nicotine may act as an antidepressant because it stimulates the release of many different neurotransmitters, but tolerance may develop quickly (32). Second, it can cause the symptoms of depression when smokers try to quit (32). Finally, twin studies have suggested that tobacco dependence is determined by a gene that makes carriers vulnerable to depression as well (32).

That antihypertensive drugs may cause depressive disorders was recognized more than 40 years ago (16). Reserpine and methyldopa are established causes of depressive disorders. We found that antihypertensive treatment at baseline was associated with depressive symptoms at follow-up. In another community-based study, low diastolic blood pressure at baseline was also associated with incident positive CES-D scores at follow-up (33). These findings suggest that lowering blood pressure itself might be causative, rather than the pharmacological entities. A strong decline of blood pressure may cause serious malaise and lassitude and this may be misclassified as depressive disorder. The fact that certain antihypertensives such as thiazide diuretics and calcium antagonists are less frequently associated with depressive disorder despite their similar effect on blood pressure reduction solves this question only partly (34-39). More detailed studies are needed in which the different kinds of antihypertensive drugs are compared. Clarification of the relationship with depression may have substantial clinical implications.

In adults and elderly, the onset of depression seems to be independent of the onset of type 2 diabetes; for type 1 diabetes, it is less clear (40-45). The risk of developing depression did not seem to be higher in patients with diabetes once complications and co-morbid diseases were accounted for (40-45). Our finding that diabetes is associated with an incident episode of minor or major depression does not concord with these earlier findings, and could thus be a chance finding. We did not find an association between total and HDL-cholesterol level and depressive symptoms or depressive disorders. This result is in line with the results of the cohort study performed by Blazer et al (46). Moreover, high total and low HDL are associated with an increased of stroke in elderly men, but not in elderly women (7). However, Kim et al found that low and high total cholesterol as well as low HDL cholesterol were associated with incident depression at two-year follow-up (13). The authors assumed that low cholesterol is associated with frailty and poor health, and thereby with depression. It is possible that our study did not have sufficient power to detect an association between serum cholesterol and depression, because statin use is high in our study population and this might give rise to a skewed distribution of total serum cholesterol levels.

Even though most individual CVRFs were not associated with depressive symptoms or depressive disorders, the Framingham stroke risk score – a composite score which encompasses the majority of the CVRFs that we studied – was associated with depressive symptoms and depressive disorders in the models for individual risk factors, and with depressive disorders in the multivariate model. This finding renders some support to the

vascular depression hypothesis. However, Lyness et al did not find a positive association between the Framingham stroke risk score and depressive disorders in a prospective study among primary care patients. This may have been due to insufficient power resulting from a small sample (N=247), a higher cut-off for depressive symptoms (21 on CES-D) and a short follow-up period of one year (47). Two other studies yielded mixed results as well for a cumulative score of vascular burden. In the population-based study, a history of two or more risk factors, i.e. self-reported heart disease, hypertension, diabetes or atherosclerosis, was not associated with depressive symptoms after one year of follow-up (14), whereas in a study among rehabilitation inpatients, two or more risk factors reported in the medical records, i.e. hypertension, diabetes or atrial fibrillation, increased the risk of depressive symptoms at 6- and 18-months of follow-up (48).

Our study allowed examination of the association between a comprehensive set of CVRFs and depression in a general elderly population. Depressive symptomatology was assessed not only with the use of a dimensional symptom rating scale but also during a clinical interview in which DSM-IV classified depressive syndromes were diagnosed. Moreover, the percentage of participants followed up was relatively high in our study. Furthermore, studies among patients presenting for treatment, be it for their depressive symptoms or other diseases, might suffer from information bias. The medical records may provide differential information on the CVRFs depending on the patient's psychiatric status. Our study avoids the information bias inherent in such studies, because all participants were assessed in the same way.

Nevertheless, a potential limitation of our study is that selection bias cannot be ruled out. The probability that a participant drops out is higher if he has more vascular health problems at baseline, or if he is depressed at the time of the follow-up examination. We excluded the 50 participants with no psychiatric work-up and this could have introduced bias and might explain some discrepancies between the multivariate models. Another limitation is that risk factors that occurred between baseline and follow-up measurement were not captured. This might have led to an underestimation of the associations. In addition, depressive episodes that occurred after baseline and disappeared before the follow-up assessment were not identified. As depressive syndromes often have a chronic and recurrent nature (49-52), these episodes most probably consisted of on average shorter episodes. There is some evidence that vascular depression episodes are less likely to be of short duration (4, 5), so that the bias as a result of missing these episodes would have yielded stronger positive associations between vascular risk factors and incident depression. Nonetheless, the limited number of incident depressive disorders could have been responsible for the negative findings with regard to this outcome. Finally, as we did not fit a separate multivariable model for each individual risk factor, our multivariable models might have been overadjusted with respect to some of these factors, such as atrial fibrillation.

In conclusion, we found that current smoking, the use of anti-hypertensive medication and diabetes mellitus were the only CVRFs that were associated with an increased risk of depressive symptoms or depressive disorders in the multivariable analyses. Apart from an ischemic effect on cerebral small vessels, these factors have also been hypothesized to cause abnormalities in neurotransmitter metabolism. All in all, we found no strong and consistent relationship between individual CVRFs and depression. On the other hand, there was a positive association between the Framingham stroke risk score and depressive disorders. This composite score encompasses many of the individual risk factors. Hence, the findings of this study provide only moderate support for the 'vascular depression' hypothesis.

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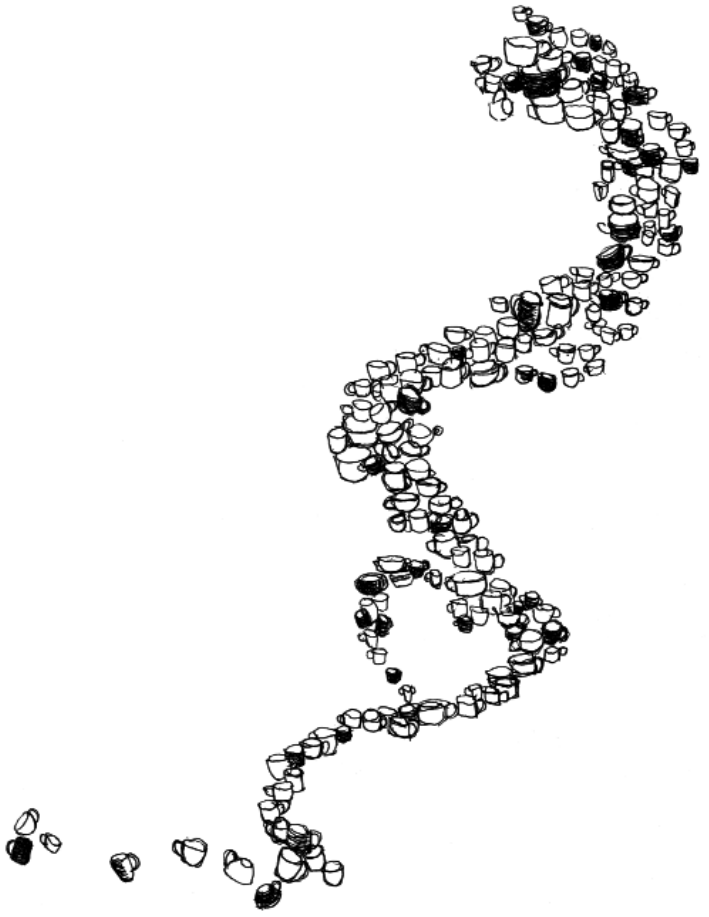
Chapter 7

Retinal vascular calibers



Abstract

Objectives. In order to test the "vascular depression" hypothesis, we investigated whether smaller retinal arteriolar or larger venular calibers, which are markers of cerebral microvascular disease, were associated with incident late-life depression.

Methods. We included 3,605 participants (>55 years) from the population-based Rotterdam Study, who were free of depression at baseline (1993-1995) and had gradable fundus photographs for retinal vascular caliber measurements. We identified persons with incident depressive symptoms and syndromes using psychiatric interviews during follow-up visits and continuous monitoring. Follow-up was complete until October, 2005.

Results. After a mean follow-up of 9.0 years, 555 participants developed depressive symptoms, including 243 with depressive syndrome. Neither smaller arteriolar (age- and sex-adjusted hazard ratio (HR): 1.01; 95%-confidence interval (CI): 0.93-1.10), nor larger venular calibers (HR: 1.02; 95%-CI: 0.94-1.12) were associated with incident depressive symptoms or syndromes.

Conclusions. Our present data showed no evidence of an association between retinal vascular calibers and incident late-life depression.

Introduction

According to the "vascular depression" hypothesis cerebral vascular pathology has been implicated in the pathogenesis of late-life depression.(1) Previous studies reported an association between depression and vascular risk factors, including white matter lesions on magnetic resonance imaging (MRI) and stroke.(1-3) However, not all studies have consistently demonstrated these associations.(4) Furthermore, it remains unclear whether macrovascular or microvascular processes are related to depression.(1-5)

The retinal microcirculation, which can be assessed non-invasively,(6) shares similar anatomical, physiological, and embryological features with the cerebral microcirculation. Studies suggest that retinal arteriolar and venular calibers are markers of cerebral microvascular disease.(6) Moreover, changes in the retinal microcirculation such as arteriolar narrowing or venular dilatation have been linked to cerebral white matter lesions on MRI scans.(6) Data both on retinal microcirculation and depression were collected in the Rotterdam Study, thereby providing an ideal opportunity to examine possible associations between microvascular disease and depression. Previously, two cross-sectional studies could not find any association between retinal vascular abnormalities (e.g. retinal vascular caliber, retinopathy signs) and prevalent depression.(7,8) Thus far, there are no prospective data on these associations. In the present study, we examined associations between retinal vascular calibers and incident late-life depression in a large prospective population-based study.

Methods

Study sample

The present study was performed as part of the Rotterdam Study, a population-based, cohort study on chronic and disabling diseases in the elderly.(9) A total of 7,983 participants aged 55 years and older and living in one district of Rotterdam agreed to participate. The study was conducted according to the tenets of the Declaration of Helsinki, and the Medical Ethics Committee of the Erasmus Medical Center approved the study protocol. A written informed consent was obtained from all participants. Up till now four visits have taken place during which participants underwent an extensive interview and a physical examination (1989-1993, 1993-1995, 1997-1999, 2002-2004). During the first visit, 5,674 participants had gradable fundus photographs and during the second visit, the baseline of the present study, 4,940 participants were screened for depressive symptoms. The study sample for the present study consisted of 3,605 persons who were free of depression at baseline and had gradable fundus transparencies for retinal vascular caliber measurement.

Retinal vascular caliber measurements

The ophthalmic examination consisted of taking fundus photographs centered on the optic disc of both eyes with a telecentric fundus camera (pharmacological mydriasis, 20° field, Topcon Optical Company, Tokyo, Japan). These photographs were digitized with a high-resolution scanner (Nikon LS-4000, Nikon Corporation, Japan) and for each participant the eye with the best image quality was analyzed with a semi-automated system (Retinal Analysis, Optimate, WI; Department of Ophthalmology and Visual Science, University of Wisconsin-Madison). Per eye one summary value was calculated for the caliber of the blood column of the arterioles and one for the venules (in micrometers). As eyes may have different magnifications in case of refractive changes due to corneal curvature, lens and axial length differences, we additionally adjusted these summary vessel measures with Littmann's formula to approximate absolute measures. Four trained graders performed all measurements masked for participant characteristics. Both inter- and intragrader studies showed good to excellent agreement (intraclass correlation coefficient = 0.49–0.95).(6)

To examine whether we could extrapolate caliber measurements from the first to the second examination round (baseline of present study), we examined differences in vascular calibers over time. We measured the calibers in a random subset of 303 participants who had gradable fundus photographs from the first and the third examination round that covered a mean interval of six years. The mean differences were -0.82 µm (95% confidence interval (CI): -2.40; 0.77) for arteriolar calibers and -0.31 µm (95% CI: -2.47; 1.86) for venular calibers.

Assessment of depression

At baseline, participants were screened for depressive symptoms with either the validated Dutch version of the Center for Epidemiologic Studies Depression Scale (CES-D) or the validated Dutch version of the Hospital Anxiety and Depression Scale (HADS).(10) Persons with a score of 16 or higher on the CES-D or 9 or higher on the HADS were considered screen-positive.

During follow-up visits, information on incident depressions was obtained from psychiatric examinations that consisted of a screening with the CES-D, and subsequent semi-structured interviews of the screen-positive participants (Schedules for Clinical Assessment in Neuropsychiatry (SCAN)). Additionally, the self-reported history of depression was solicited. Moreover, the general practitioner's medical records and pharmacy records were continuously monitored for depressions and use of anti-depressants by automated linkage of these records with the study database.(10)

We categorized depressions as (1) episodes of clinically relevant depressive symptoms, if at least one clinically relevant core symptom of major depression (feeling depressed or loss-of-interest) had been reported during the psychiatric interview or in the medical record, or as (2) depressive syndromes, which included major and minor depression and dysthymia

according to the criteria of Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association (fourth edition), as well as depressions diagnosed by a general practitioner or other physician, and self-reported depressions that had been treated by a health professional.(10) Follow-up was complete until October 1st, 2005. We defined the date-of-onset as the day of the first report of symptoms, or the first prescription date of an antidepressant drug, whichever came first.

Cardiovascular risk factors

Confounders such as age, sex, smoking, blood pressure, diabetes mellitus, body mass index, carotid artery plaques and serum cholesterol levels were measured as described previously.(6)

Statistical analyses

Associations of retinal vascular calibers with incident late-life depression were analyzed by means of Cox proportional hazards models. Hazard ratios (HR), 95% confidence intervals (CI) and Wald chi-square (χ^2) test statistics with one degree of freedom for depression were calculated by analyzing retinal vascular calibers both linearly (per standard deviation (SD)) and in quartiles. Persons were followed-up until onset of depressive symptoms or depressive syndromes, dementia, death, loss to follow-up, or October 1st, 2005, whichever came first. All analyses were performed using SPSS (Windows version 15.0).

Results

After a mean follow-up of 9.0 years, 555 persons (15.4%) developed an incident late-life depression, of whom 312 (8.7%) suffered from depressive symptoms and 243 (6.7%) had a depressive syndrome. Table 1 presents characteristics of the participants that were obtained at the time of the retinal vascular caliber measurements.

Neither smaller retinal arteriolar (age- and sex-adjusted HR per SD decrease: 1.01; 95% CI: 0.93-1.10; Wald χ^2: 0.036; p-value: 0.85) nor larger venular calibers (age- and sex-adjusted HR per SD increase: 1.02; 95% CI: 0.94-1.12; Wald χ^2: 0.262; p-value: 0.61) were associated with an increased risk of depressive symptoms. The corresponding age- and sex-adjusted HR for depressive syndromes were 1.08 (95% CI: 0.94-1.22; Wald χ^2: 1.242; p-value: 0.27) for arteriolar caliber and 1.00 (95% CI: 0.88-1.14; Wald χ^2: 0.001; p-value: 0.97) for venular caliber. Categorizing retinal vascular calibers into quartiles did not show a consistent trend towards a higher risk of incident depression. Additional adjustment for other cardiovascular risk factors did not alter the associations. Also, excluding persons with history of depression before the second examination round (n=1,092) did not change the above-mentioned results.

Table 1 Characteristics of the study population at time of retinal vascular caliber measurements (1990-1993)

	Participants	Non-participants*	Adjusted differences† (95% CI)‡
Number (n)	3,605	2,069	
Age (years)	66.1 (7.1)	71.4 (8.9)	5.3 (4.9; 5.7)§
Gender (% women)	55	66	9.5 (6.7; 12.3)§
Institutionalized (%)	1	8	2.6 (1.7; 3.6)§
Diabetes mellitus (%)	8	13	2.0 (0.0; 3.6)§
Smoking (% current)	22.6	25.4	8.1 (5.7; 10.5)§
Body mass index (kg/m^2)	26.3 (3.5)	26.4 (3.9)	-0.02 (-0.19; 0.23)
Systolic blood pressure (mmHg)	137.3 (21.4)	140.7 (23.1)	0.27 (-1.51; 0.96)
Diastolic blood pressure (mmHg)	74.0 (11.1)	73.0 (11.8)	-0.30 (-0.95; 0.35)
Number of carotid artery plaques ≥ 4 (%)	13.3	21.1	4.6 (2.3; 6.8)§
Serum total cholesterol (mmol/l)	6.63 (1.17)	6.65 (1.26)	0.05 (-0.02; 0.11)§
Serum HDL‖ cholesterol (mmol/l)	1.35 (0.36)	1.35 (0.37)	-0.02 (-0.04; 0.00)
Retinal arteriolar caliber (µm)	147.0 (14.2)	146.5 (14.9)	0.66 (-0.17; 1.47)
Retinal venular caliber (µm)	222.7 (20.3)	220.6 (21.8)	0.97 (-0.20; 2.13)

Presented as means (standard deviation) or percentages

* Non-participation at the second examination round, including prevalent depression cases (1993-1995)

† Age and sex adjusted if applicable

‡ CI = confidence interval

§ Statistically significant ($p<0.05$)

‖High-density lipoprotein

Discussion

In this prospective population-based cohort study of elderly persons, we did not find an association between retinal vascular calibers and incident late-life depressive symptoms or depressive syndromes.

So far, studies examining the associations between microvascular processes and depression used MRI-markers such as white matter lesions and brain infarcts. These studies produced inconsistent findings probably due to differences not only in assessment of depression, source population or study design, but also differences in MRI acquisition and grading.(2-4)

Two recent studies used retinal microvasculature to explore the association between microvascular disease and depression.(7,8) Population-based data from the Cardiovascular Health Study among 2,420 persons aged 65 years and older showed that persons with generalized arteriolar narrowing or generalized venular dilatation were not more likely to have depression.(7) Also, other microvascular signs were not related to the presence of depression either.(7) More recently, a clinic-based study including 99 participants showed

that diabetic patients with major depression (*n*=34; 145.3µm) had statistically significantly larger retinal arteriolar caliber compared to diabetic patients without depression (*n*=27; 139.2µm) and healthy persons (*n*=38; 132.6µm).(8) However, after additional adjustment for vascular risk factors this trend became non-significant. Findings from these cross-sectional studies are in accordance with the results we found in the current prospective study.

The lack of an association should be interpreted within the context of several possible limitations of the present study. Firstly, the retinal vascular caliber measurements were performed on average two years prior to the initial assessment of prevalent depression. This might have introduced selection bias if the retinal vascular calibers were different at the time of the baseline assessment of depression compared to the actual measurements. However, in the random subset, we did not find any significant differences in vascular calibers over a six-year period, suggesting a limited role for selection bias. Secondly, some persons who developed depression during follow-up already had a history of depression. As depression is a risk factor for vascular disease as well as for recurrent depression any possible true effect would most likely have been overestimated. However, excluding persons with history of depression did not alter our findings. Thirdly, other retinal microvascular signs such as arteriovenous nicking and focal arteriolar narrowing were not examined in the present study. Finally, as depression is a remitting and relapsing disease, it is a challenge to ascertain all episodes of this disease which occur in between follow-up examination rounds. We attempted to limit the underdetection of depression by continuously monitoring the general practitioner's medical records and pharmacy records.

Strengths of our study include the population-based setting, the longitudinal design of the study with on average nine years of follow-up and standardized procedures for retinal vascular caliber measurements. Due to the close collaboration with general practitioners and other health care institutions, the follow-up for depressive episodes was virtually complete. Finally, with a two-sided alpha of 0.05 and a sample size of 3,605, we had a power of 80% to show a significant relative risk of at least 1.2 per standard deviation change in vascular calibers.

In conclusion, our present data show no evidence of an association between retinal vascular calibers and incident late-life depression.

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Chapter 8

MRI-markers of vascular brain disease

Abstract

Background. Whereas cross-sectional studies show an association between vascular brain disease and depression, longitudinal data are scarce. In a population-based study we investigated this relationship both cross-sectionally and longitudinally.

Methods. 479 persons (60-90 years) underwent brain MRI. Brain atrophy, white matter lesions (WML) and brain infarcts reflected vascular brain disease. At baseline (1995-1996) and follow-up examinations we identified persons with depressive symptoms and syndromes using CES-D and psychiatric interview. Moreover, medical records were continuously monitored to identify incident depression. Follow-up was complete until October 2005.

Results. At baseline 36 persons had depressive symptoms. Brain atrophy, WML, and infarcts were associated with presence of depressive symptoms. During follow-up 92 persons developed depressive symptoms, of whom 35 depressive syndrome. There was no association of any MRI-marker with incident depressive symptoms or syndromes.

Conclusions. Markers of vascular brain disease were associated with depression cross-sectionally. However, no relationship was present between these markers and risk of depression longitudinally.

Introduction

Vascular disease and depression in the elderly are closely related.[1,2] This has fuelled the 'vascular depression' hypothesis,[3] which postulates a vascular basis of late-life depression.[4-6] With magnetic resonance imaging (MRI) markers of vascular brain disease can be visualized, including white matter lesions (WML), brain infarcts, and brain atrophy. Various cross-sectional studies reported an association of several MRI-markers with depression.[4,7-10] Longitudinal studies thus far only investigated the relationship of WML with depression longitudinally, and found inconsistent results.[9,11-13] We investigated the relationship of several MRI-markers of subclinical vascular brain disease both cross-sectionally with prevalent depression, and longitudinally with new-onset depression

Methods

Study population

This study is based on an age-stratified (60-90 years) sample of 563 participants from the population-based Rotterdam Study,[14] who underwent multi-sequence brain MR-imaging in 1995-1996.[15] The institutional medical-ethics committee approved the study and all participants gave written informed consent. Of the 563 participants, 73 did not complete MRI-examination due to claustrophobia or technical reasons, and 4 persons did not undergo psychiatric assessment at baseline. Furthermore, of the eleven persons using anti-depressants at baseline seven had no depressive symptoms. These seven persons were excluded, because we could not determine whether the indication for using this medication was still present. Therefore, a total of 479 persons were available for the analysis.

MRI measures at baseline

Image acquisition, classification algorithm, and validation steps have been described elsewhere.[15] In summary, we used the k-nearest-neighbor classifier to classify voxels into cerebrospinal fluid, grey matter, normal white matter, and WML. Using non-rigid transformation, non-cerebral tissues were stripped. For measurement of lobar and deep central brain volumes, we created an atlas, in which the lobes were labeled according to a slightly modified version of the segmentation protocol as described by Bokde et al.[16] Subsequently, we used validated non-rigid transformation to transform this atlas to each brain. Brain infarcts were rated visually as focal hyperintensities on T2-weighted images, 3 mm in size or larger and with a corresponding prominent hypointensity on T1-weighted images.[15]

Assessment of depression

The assessment of depression has been described elsewhere.[17] At the baseline visit and during three follow-up rounds (1997-1999, 1999-2000, 2000-2001) the Center for Epidemiological Studies Depression Scale (CES-D) was used as screening tool with a cut-off of 16. Screen-positive individuals then underwent the Present State Examination [18] to diagnose major depression, dysthymia, and minor depression. The response rate at each of the three follow-up rounds was 95% (437 of the 461 eligible), 81% (336 of 414 eligible), and 81% (309 of 381 eligible). Moreover, medical and pharmacy records of participants (e.g. hospital discharge letter, specialists' reports, and notes of general practitioners) were continuously monitored for depressive episodes and for start of anti-depressants during the follow-up period by automated linkage of the general practitioners' and pharmacists' records with the database. These data ensured virtually complete follow-up among care-seeking participants.

Depressive episodes were classified as *depressive symptoms* if persons were CES-D positive; or had at least one core symptom of depression recorded in medical files; or started anti-depressants (without documentation of clinical symptoms). Depressive symptoms were further classified as *depressive syndrome* if persons were diagnosed as suffering from major depression, minor depression, or dysthymia according to the psychiatric interview or medical files. Follow-up for incident depressive symptoms and syndromes was complete until October 1st 2005.

Covariates

Covariates included education, smoking, blood pressure, diabetes mellitus, body-mass index, and intima-media thickness.[15]

Statistical analysis

All volumes were expressed as percentage of intra-cranial volume. Total white matter was the sum of normal white matter and WML. WML were analyzed as ln(WML volume), because of the skewed untransformed measures. We used logistic regression to calculate odds ratios for presence of depressive symptoms associated with brain imaging markers. We also performed cross-sectional analyses with linear regression using CES-D score continuously. For the longitudinal analyses, we excluded persons with depressive symptoms at baseline (n=36). We used Cox' proportional-hazards models to calculate hazard ratios (HR) for incident depressive symptoms or syndromes associated with brain imaging markers. Persons were followed until onset of depressive symptoms or syndromes, loss to follow-up, or October 1st 2005, whichever came first.

Results

Table 1 shows the baseline characteristics of the study population. Thirty-six persons had depressive symptoms, of whom 6 had a depressive syndrome. The smaller the brain volume the more likely persons were to have depressive symptoms (table 2). At the lobar level, particularly parietal and temporal lobe atrophy were associated with depressive symptoms. The likelihood of having depressive symptoms increased with increasing volume of WML, especially in the frontal lobe and deep central region, and with presence of brain infarcts. Parietal lobe atrophy and deep white matter lesions were also related to CES-D continuously (table 2). Numbers were too small to perform separate analyses for prevalent depressive syndromes (n=6).

Table 1 Baseline characteristics of the study population

N	479
Age, yr	73.4 (7.8)
Women	50%
Primary education only	30%
MMSE, score	27.7 (2.1)
Current smokers	18%
Former smokers	54%
Systolic blood pressure, mmHg	146 (21)
Diastolic blood pressure, mmHg	77 (12)
Diabetes mellitus	5.0%
Body mass index, kg/m2	26.2 (3.5)
Intima media thickness, mm	0.87 (0.14)
MRI markers	
Whole brain volume, %ICV	77.4 (3.6)
Frontal lobe volume, %ICV	27.4 (1.9)
Parietal lobe volume, %ICV	15.8 (1.1)
Occipital lobe volume, %ICV	9.0 (0.7)
Temporal lobe volume, %ICV	15.5 (0.9)
Deep central region*, %ICV	9.7 (0.5)
Grey matter, %ICV	46.6 (4.1)
Normal white matter, %ICV	29.5 (6.3)
Total white matter, %ICV	30.8 (5.7)
White matter lesions, %ICV	1.33 (1.51)
Brain infarcts	28%

Values are percentages or means (standard deviation); MMSE stands for Mini-Mental State Examination, ICV for Intra-cranial volume; * The deep central region includes the corpus callosum, insular cortex, basal ganglia, and the white matter surrounding the basal ganglia.

During 3,373 person-years of follow-up (mean 7.5 years) a total of 92 persons developed depressive symptoms, of whom 35 suffered from a depressive syndrome. Neither global nor lobar brain tissue volumes were associated with incident depressive symptoms or syndromes (table 3 and 4). Furthermore, neither WML nor brain infarcts were associ-

ated with incident depressive symptoms or depressive syndromes. Additional adjustment for cardiovascular risk factors did not change the results.

Table 2 Cross-sectional association between brain tissue volumes and prevalent depressive symptoms (n=36), including depressive syndromes (n=6)

Brain tissue volumes*	Odds-ratio of being CES-D positive (score of 16 is taken as cut-off)	Difference in CES-D score (using CES-D score continuously)
Global brain tissue volumes		
Whole brain volume	0.52 (0.31-0.87)	-0.71 (-0.15; 0.03)
Grey matter	0.95 (0.67-1.33)	-0.02 (-0.58; 0.54)
Normal white matter	0.70 (0.46-1.07)	-0.52 (-1.16; 0.13)
Total white matter	0.80 (0.53-1.21)	-0.30 (-0.92; 0.32)
Lobar brain tissue volumes†		
Frontal lobe	0.68 (0.43-1.07)	-0.65 (-1.32; 0.03)
Parietal lobe	0.56 (0.35-0.90)	-0.65 (-1.30; -0.01)
Occipital lobe	0.87 (0.60-1.26)	-0.09 (-0.66; 0.48)
Temporal lobe	0.65 (0.43-0.98)	-0.33 (-0.96; 0.31)
Deep central region	1.08 (0.75-1.53)	0.36 (-0.20; 0.93)
WML volume‡ and brain infarcts		
Global WML	1.56 (0.98-2.46)	0.41 (-0.20; 1.02)
Frontal WML	1.68 (1.07-2.62)	0.45 (-0.14; 1.04)
Parietal WML	1.30 (0.85-1.99)	0.11 (-0.47; 0.68)
Occipital WML	1.45 (0.94-2.23)	0.37 (-0.22; 0.95)
Temporal WML	1.36 (0.89-2.08)	0.38 (-0.22; 0.96)
Deep WML	1.83 (1.13-2.96)	0.72 (0.12; 1.32)
Brain infarcts (yes versus no)	2.35 (1.12-4.91)	0.82 (-0.46; 2.09)

WML stands for white matter lesion, CES-D for Center for Epidemiological Studies Depression Scale; * expressed per standard deviation increase; † these volumes included grey matter and total white matter together; ‡ all white matter lesion volumes were natural log transformed.

Discussion

In this population-based cohort study of elderly persons we found that structural markers of vascular brain disease were cross-sectionally related to presence of depressive symptoms. However, we did not find any association between structural brain markers and incident depressive symptoms or depressive syndromes.

Strengths of our study include the population-based setting, and the cross-sectional as well as longitudinal design of the study with more than seven years of follow-up. Moreover, contrary to other studies we investigated various markers of vascular brain disease using automated quantification techniques. A limitation is that we lacked reliable data on depression before baseline. Therefore, some persons may already have had a depression before baseline. However, given that persons with a history of depression have an increased risk of recurrent depression, together with the strong cross-sectional association between

Table 3 Risk of depressive symptoms and syndromes associated with brain tissue volumes

Brain tissue volumes*	Hazard ratio (95% CI) for incident depressive symptoms (including depressive syndromes) (N=92)	Hazard ratio (95% CI) for incident depressive syndromes (N=35)
Global brain tissue volumes		
Whole brain volume	1.06 (0.79-1.42)	0.89 (0.55-1.42)
Grey matter	0.92 (0.75-1.14)	0.97 (0.69-1.37)
Normal white matter	1.10 (0.86-1.41)	0.93 (0.62-1.40)
Total white matter	1.10 (0.87-1.40)	0.98 (0.66-1.44)
Lobar brain tissue volumes†		
Frontal lobe	0.89 (0.69-1.16)	0.90 (0.59-1.38)
Parietal lobe	1.05 (0.83-1.34)	0.90 (0.60-1.33)
Occipital lobe	1.08 (0.87-1.34)	1.09 (0.78-1.53)
Temporal lobe	1.15 (0.91-1.45)	0.88 (0.60-1.30)
Deep central region	1.10 (0.89-1.38)	1.00 (0.69-1.46)
WML volume‡ and brain infarcts		
Global WML	0.88 (0.71-1.10)	0.83 (0.59-1.18)
Frontal WML	0.87 (0.71-1.08)	0.84 (0.60-1.17)
Parietal WML	0.88 (0.72-1.07)	0.87 (0.64-1.19)
Occipital WML	0.88 (0.71-1.09)	0.87 (0.62-1.22)
Temporal WML	0.92 (0.74-1.14)	0.87 (0.62-1.22)
Deep WML	0.92 (0.74-1.16)	0.89 (0.62-1.27)
Brain infarcts (yes versus no)	0.86 (0.51-1.44)	0.88 (0.36-2.11)

Values are adjusted for age, sex, and education. Persons were censored at onset of depressive syndrome, onset of depressive symptoms, date last known to be alive in case of loss to follow-up, or October 1st 2005, whichever came first.
CI stand for confidence interval, WML for white matter lesion; * expressed per standard deviation increase; † these volumes included grey matter and total white matter together; ‡ all white matter lesion volumes were natural log transformed.

vascular brain disease and depression, longitudinal analyses would overestimate any true effect. Another limitation is possible selection-bias due to differential follow-up. If persons with vascular disease compared to those without were more prone to seek medical help, estimates from longitudinal analyses could easily overestimate effects. Conversely, if these persons are less likely to report depressive symptoms, it would lead to an underestimation. A final consideration is that we excluded persons who used anti-depressants at baseline. However, *post hoc* analyses including these persons in either the depressed or non-depressed group yielded unchanged results.

In our cross-sectional analyses we found brain atrophy, brain infarcts and WML to be related to depressive symptoms (including depressive syndromes). This fits well with various previous studies.[4,8,9] Furthermore, our results concur with published data showing that particularly atrophy in the parietal and frontal lobes, and frontal and deep WML are related to depression.[4,10,19]

In contrast, longitudinally we found no association between MRI-markers and incident depression. Although we have to be cautious to interpret these as null associations because of the relatively wide confidence intervals, the HR are pretty close to 1 and do not suggest

any major effect. If anything, most are in the opposite direction of what is expected based on the vascular depression hypothesis, namely that larger brain volume is associated with a *de*creased risk of depression (HR below 1), and WML with an *in*creased risk of depression (HR above 1).

Table 4 Risk of depressive symptoms and syndromes associated with brain tissue volumes, based on only survey data.

Brain tissue volumes*	Hazard ratio (95% CI) for incident depressive symptoms (including depressive syndromes) (N=35)	Hazard ratio (95% CI) for incident depressive syndromes (N=18)
Global brain tissue volumes		
Whole brain volume	1.24 (0.76-2.01)	1.30 (0.67-2.53)
Grey matter	0.82 (0.59-1.14)	0.85 (0.53-1.34)
Normal white matter	1.34 (0.59-1.14)	1.29 (0.74-2.25)
Total white matter	1.32 (0.90-1.93)	1.31 (0.77-2.23)
Lobar brain tissue volumes†		
Frontal lobe	1.19 (0.77-1.84)	1.35 (0.75-2.45)
Parietal lobe	1.06 (0.70-1.58)	1.05 (0.60-1.83)
Occipital lobe	1.10 (0.79-1.54)	1.07 (0.67-1.70)
Temporal lobe	1.08 (0.72-1.48)	1.04 (0.61-1.80)
Deep central region	1.03 (0.72-1.48)	1.05 (0.63-1.75)
WML volume‡ and brain infarcts		
Global WML	0.76 (0.53-1.08)	0.79 (0.48-1.29)
Frontal WML	0.76 (0.55-1.04)	0.78 (0.50-1.22)
Parietal WML	0.82 (0.60-1.13)	0.86 (0.55-1.35)
Occipital WML	0.89 (0.63-1.27)	0.86 (0.53-1.38)
Temporal WML	0.87 (0.61-1.23)	0.92 (0.56-1.52)
Deep WML	0.79 (0.55-1.23)	0.89 (0.53-1.50)
Brain infarcts (yes versus no)	0.75 (0.33-1.73)	0.83 (0.26-2.70)

Values are adjusted for age, sex, and education. Persons were censored at onset of depressive syndrome, onset of depressive symptoms, date last known to be alive in case of loss to follow-up, or October 1st 2005, whichever came first.
CI stands for confidence interval, WML for white matter lesion; * expressed per standard deviation increase; † these volumes included grey matter and total white matter together; ‡ all white matter lesion volumes were natural log transformed

Several explanations for null associations in our longitudinal analyses need to be considered. Firstly, our study design implies a time delay between baseline vascular damage and onset of depression. However, it is possible that vascular injury directly leads to depressive symptoms without any delay. A second explanation might be that the causal pathway works the other way around, i.e. depression causes vascular brain disease. Based on only limited data on progression of white matter lesions, we did not find any such association in the Rotterdam Scan Study (data not shown). However, two studies have reported a larger increase in WML in depressed compared with non-depressed persons.[9,12] Though it is not established how depression could lead to vascular brain disease and brain atrophy, possible mechanisms include platelet dysfunction, hypotensive episodes, unhealthy lifestyle

choices, and elevated cortisol levels in the brain, which in turn can cause glucocorticoid-mediated neurotoxicity.[1,5,20] However, it is unclear why depression would cause vascular disease only in specific areas in the brain, e.g. frontal and deep central WML. Thirdly, it is possible that vascular brain injury does not relate to incidence of first depression, but to persistent, chronic, relapsing, or recurrent depression. To test these possibilities, future studies should seek to discern more clearly first-ever depressions from possible recurrent events and accurately establish the duration of the depressive episode. Finally, a common etiology, e.g. genetic predisposition, could link depression with vascular brain disease cross-sectionally, but not necessarily longitudinally. Indeed, a twin study showed that the co-occurrence of cardiovascular disease and depression is partly explained by common genetic risk factors.[21]

In conclusion, we found that MRI-markers of vascular brain disease were strongly associated with depression cross-sectionally. However, our study emphasizes that a cross-sectional association does not necessarily demonstrate causation, as we found no evidence for the 'vascular depression' hypothesis relating these brain markers to incident depression. Still, more longitudinal studies are needed to precisely elucidate this hypothesis. After all, even a non-causal relation of vascular disease with depression might point towards possibilities for prevention and treatment that thus far have remained unexplored.

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Chapter 9

Transient ischemic attacks

Abstract

Context. Depression after stroke is common. Like stroke, transient ischemic attacks (TIAs) are manifestations of long-term atherosclerotic damage to the brain. However, the risk of developing a depression after a TIA is unknown.

Objective. To study whether TIAs increase the risk of incident late-life depression.

Design, setting and participants. A cohort study of 5,095 inhabitants of Rotterdam, the Netherlands. Participants were aged 56 years or older and free of depression at baseline. Follow-up duration was on average 8 years.

Data assessment methods. TIAs and depressions were identified through regular standardized examinations and continuous monitoring of medical and pharmaceutical records. Attacks that presented with focal symptoms only (focal attacks) were distinguished from attacks that were accompanied by nonfocal symptoms (mixed attacks), and attacks that presented with nonfocal symptoms only (nonfocal attacks). Depressive episodes were categorized as (1) DSM-IV defined depressive disorders, (2) other depressive syndromes, and (3) clinically relevant depressive symptoms.

Main Outcome Measure. We estimated hazard ratios (HR) with time-varying Cox regression analyses, adjusting for socio-demographic and health related factors, such as incident stroke.

Results. TIAs were significantly associated with the risk of incident depressive disorders and other syndromes (HR 1.68; 95% CI 1.12-2.51), and depressive disorders only (HR 2.42; 95% CI 1.26-4.67). We also found an almost three-fold increased risk of DSM-defined depressive disorders in persons without a history of depression at baseline (HR 2.91; 95% CI 0.96-8.81). In contrast to focal and mixed attacks that comprise TIAs, nonfocal attacks were not related to depression. Including depressive symptoms in the case definition of depression diluted the estimated risk of TIAs.

Conclusions. TIAs are independently associated with an increased risk of incident depression. Our findings suggest that symptomatic cerebrovascular disease, in particular when located in cortical brain regions, may predispose to late-life depression.

Introduction

Stroke is a common major vascular event in late-life. It often results in permanent damage to the brain and reduced functional status. Up to 50% of patients develop depression in the first month after a stroke (1, 2), and the risk of depression remains high in the following year (3). Depression after stroke not only decreases the quality of life for the patient but can substantially contribute to the burden of disease for primary care givers (4). Like stroke, transient ischemic attacks (TIAs) are common clinical manifestations of long-term atherosclerotic damage to the brain, but, per definition, TIAs do not give rise to permanent functional disabilities. Rather, TIAs are characterized by sudden neurological symptoms that completely resolve within 24 hours (5). The possible risk of depression after a TIA has received far less attention than the risk conveyed by stroke. To our knowledge, investigations of TIAs and depression are limited to cross-sectional studies. In a clinical study, the prevalence of major depressive disorder in patients with carotid stenosis and TIA (40%) was significantly higher than in the control group (0%) (6). This finding was confirmed in a small population-based study (7). Although studies using a cross-sectional design cannot rule out that the observed depressions occurred prior to the cerebrovascular attack (8-10), longitudinal studies based on accurate assessments of the onset of depression are lacking.

The vascular depression hypothesis posits that cerebrovascular disease may predispose, precipitate or perpetuate late-life depression (11, 12). Atherosclerotic lesions to brain circuits responsible for affective regulation are assumed to form the central pathology (13). The hypothesis was formulated when multiple imaging studies showed that lesions in gray matter, frontal deep white matter, and basal ganglia, as well as atrophy were more prevalent in depressed patients than in controls (14). An association between TIAs and incident depression would support the vascular depression hypothesis.

In the traditional definition, TIAs present with focal neurological symptoms (5), but transient neurological attacks that are characterized by focal and nonfocal symptoms are often diagnosed by neurologists and general practitioners as a TIA as well (15, 16). Recently, it has been proposed to define a more encompassing classification of transient neurological attacks that distinguishes between transient neurological attacks with focal symptoms, nonfocal symptoms, or a mix of both for scientific and clinical purposes. Nonfocal attacks have been associated with stroke and dementia (15), like TIAs (17) , although earlier studies indicated a more benign prognosis (18-23). Moreover, in contrast to TIAs (24), nonfocal attacks have not been associated with myocardial infarction or mortality (15). Mixed attacks seem to have the poorest prognosis in terms of vascular morbidity and mortality (15). The prognostic differences between the attacks may originate from variation in pathogenesis or localization. Distinguishing between TIAs and nonfocal attacks might provide further insight into the etiology of late-life depression.

The aim of the present study was to assess whether TIAs like stroke are associated with an increased risk of developing depression. In addition, we assessed the association between attacks with focal symptoms, nonfocal symptoms or a mix of both and incident depression. The study was performed in a large cohort of community-dwelling elderly persons free of depression at baseline. During the follow-up period, which was 8 years on average, participants were continuously monitored for the occurrence of TIAs and incident depression.

Methods

Setting

This study was embedded in the Rotterdam Study, a prospective study that started in 1989 among 7,983 inhabitants of Ommoord, a district of Rotterdam (25). Participants were 55 years of age or older. The study focuses on the occurrence and determinants of chronic diseases in the elderly. The Medical Ethics Committee of Erasmus Medical Center Rotterdam approved the study and written informed consent was obtained from all participants. Until 2004 four examination rounds took place, during which participants underwent an extensive interview and a physical examination. In addition, continuous monitoring for major events, such as TIA and depression, took place from baseline onwards through automated linkage with the medical files from the general practitioners. Information on vital status was obtained bimonthly from the municipal authorities in Rotterdam.

Study population

The study population for analysis consisted of persons at risk of incident depression and was selected as follows. During the second examination round, the baseline of the current analysis, 5769 participants were screened for depressive symptoms. Participants filled out either the validated Dutch version of the Center for Epidemiologic Studies Depression Scale (CES-D) or the validated Dutch version of the Hospital Anxiety and Depression Scale (HADS) (26, 27). Persons with a score of 16 or higher on the CES-D or 9 or higher on the HADS were considered screen-positive. At baseline, we excluded 549 persons with depressive symptoms, 105 persons with dementia, 9 persons with bipolar disorder, 2 persons lost to follow-up directly after screening, and 9 persons with unknown stroke status. This resulted in a study population of 5095 persons free of depression at baseline.

Assessment of incident depression

Assessment of depression has been described in detail before (28). Information on the occurrence of incident depressions during follow-up was obtained from (1) psychiatric examinations, (2) self-reported histories of depression, and (3) medical records. The psy-

chiatric examination during examination rounds consisted of a screening with the CES-D. Subsequently, a trained clinician conducted a semi-structured interview (Schedules for Clinical Assessment in Neuropsychiatry) in the screen-positive participants to obtain DSM-IV defined diagnoses (29),(30). The self-reported history of depression, solicited during examination rounds, included standardized questions to ascertain whether and when participants had suffered from a depressive episode, and if so whether they had been treated. Trained research-assistants scrutinized the general practitioners' medical records and copied the information about a potential depression. Two research physicians independently assessed this information according to a predefined protocol, and discussed discordant assessments.

Based on these sources, we categorized depressive episodes as either:

(1) depressive disorders, that is DSM-IV-defined major depressive disorder or dysthymia as diagnosed by a psychiatrist or another mental health professional;
(2) 'other depressive syndromes', that is a depression recorded by a general practitioner, self-reported depression for which the participant consulted a health professional, or DSM-IV-defined minor depression; or,
(3) 'clinically relevant depressive symptoms', if at least one clinically relevant core symptom of major depression had been reported.

We defined the date-of-onset as the day of the first report of symptoms according to one of the sources described above, or the first prescription date of an antidepressant drug, whichever came first.

Assessment of TIAs and stroke

Assessment procedures for TIAs and stroke have been described elsewhere in detail (15). Prevalent and incident TIAs were ascertained by a research physician who screened all participants by asking for transient neurological symptoms during examination rounds. In addition, research physicians reviewed the information from the medical files, and if available brain imaging results from hospital records. An experienced neurologist verified all diagnoses. Follow-up for all events was completed until October 1, 2005, for 96 % of potential person-years.

To ascertain a TIA, focal symptoms had to have set in suddenly and to have cleared up within seconds to a maximum of 24 hours. Attacks that presented with focal symptoms only were classified as 'focal attacks', attacks accompanied by focal and nonfocal symptoms were classified as 'mixed attacks', and attacks with nonfocal neurological symptoms only as 'nonfocal attacks' (15). A stroke was diagnosed if a patient had typical symptoms that lasted longer than 24 hours (31).

Focal brain symptoms included hemiparesis, hemihypesthesia, dysphasia, dysarthria, amaurosis fugax, hemianopia, hemiataxia, diplopia, or vertigo. The nonfocal brain symptoms included decreased consciousness, unconsciousness, confusion, amnesia, un-

steadiness, nonrotatory dizziness, positive visual phenomena, cardiac or vegetative signs, paresthesias, bilateral weakness, or unwell feelings. The date-of-onset of an incident attack was determined with the information from the sources described above. History of TIA at baseline was positive if a TIA had occurred before baseline interview. Participants that had a history of stroke at baseline or an incident stroke after baseline could not be identified with a TIA anymore.

Covariables

The following baseline covariates were considered potential confounders: age, sex, socio-economic status, disability in activities of daily living, history of depression, smoking, and hypertension. In addition, diabetes mellitus, history of cardiovascular disease, atrial fibrillation, and current use of antihypertensive medication were included as time-varying covariables.

Socio-economic status was determined in terms of the combination of highest education attained and net income (32). Disability in activities of daily living was assessed with the Modified Stanford Health Assessment Questionnaire (33). Self-reported smoking use was categorized into none, former, and current. The average of the two blood pressure measurements in sitting position was used for our analysis. The criteria for diabetes mellitus were: fasting plasma glucose level of 7.0 mmol/l or over, non-fasting glucose or an oral glucose tolerance test result of 11.1 mmol/L or over, or treatment with an antidiabetic medication or diet (34). History of cardiovascular disease encompassed angina pectoris and claudicatio intermittens, both established with the Rose questionnaire, as well as a history of myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty and peripheral artery bypass graft, as verified in the medical files (35). Information on the use of antihypertensive medication was obtained from the online pharmaceutical database described above. We included diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, and a miscellaneous group including reserpine, methyldopa and clonidine. We distinguished between non-use and current use on the day an event occurred.

Statistical analysis

To study the effect of TIAs on the risk of incident depression, we estimated hazard ratios with Cox proportional hazards analyses. We performed the analyses with three increasingly stringently defined outcomes: time to depressive syndromes and symptoms (categories 1, 2 and 3), depressive syndromes (categories 1 and 2), and depressive disorders (category 1). The exposure of having had a TIA or stroke compared to no cerebrovascular event was entered in the model as a time-varying variable. For each outcome defined above, we fitted a model that included the exposure and the confounders described above. We thus obtain risk estimates that reflect the direct effects of TIAs on the risk of depression, not through

stroke. Additionally, in order to further ascertain the chronological relationship between TIAs and depression, we repeated the models in persons without a history of depression at baseline.

Finally, we fitted a model in which each first occurrence of a focal, mixed or nonfocal attack was entered as a time-varying exposure variable, again adjusted for intermediate stroke and all confounders.

In all analyses, each participant contributed person-years from baseline date until follow-up ended when a depression occurred, dementia, death, loss-to-follow, or the end of study period on October 1, 2005. Two-sided p-values of <0.05 were considered statistically significant. For all statistical analyses we used SPSS for Windows, version 13.0.

Results

Table 1 presents the baseline characteristics of the study population. The average age was 70 years with a range of 56 to 101 years and 58 % of the participants were female. The most prevalent cardiovascular risk factor was history of smoking with 51% former smokers and 17 % current smokers. At baseline, 1641 participants had a history of depression. One or more TIAs were diagnosed in 86 participants before baseline, and in 239 persons during follow-up.

Table 1 Baseline characteristics of study population (n=5095)

	Descriptives
Age, mean (SD)	70.0 (8.3)
Female sex, n (%)	2939 (57.7)
Education, primary school only, n (%)	934 (18.3)
Income, median (range)	2690 (750-7000)
Disability, mean (range)	1.3 (1.0-4.0)
History of depression, n (%)	1641 (32.2)
Smoking,	
- former smoker, n (%)	2598 (51.0)
- current smoker, n (%)	868 (17.0)
Diastolic blood pressure, mean (range)	77 (40-128)
Systolic blood pressure, mean (range)	141 (70-242)
Body mass index, mean (range)	26.5 (14.7-48.0)
Total cholesterol, mean (range)	6.6 (2.2-18.0)
HDL cholesterol, mean (range)	1.4 (0.4-6.3)
Diabetes, n (%)	537 (10.5)
History of cardiovascular disease, n (%)	1006 (19.7)
Chronic heart failure, n (%)	206 (4.0)
Use of antihypertensives, n (%)	1558 (30.6)

In our study population, a total of 736 incident depressions occurred during 42,090 person-years. Of these episodes, 407 were depressive syndromes including 103 DSM-defined depressive disorders. The mean time between the (first) TIA and a depressive syndrome was 3.3 years (SD 2.9), counting cases of TIA present at baseline from that time onward. For incident TIAs only, the mean time to a depressive syndrome was 3.1 years (SD 2.6). The mean time based on the last (incident) TIA was only a few months short of the mean time based on first (incident) TIA. Figure 1 shows the Kaplan-Meier survival curves for depressive syndromes in persons with and without a TIA. After 12 years of follow-up, twice as many participants with a TIA had developed a depressive syndrome.

Figure 1 Cumulative survival for incident depressive syndromes by TIA status

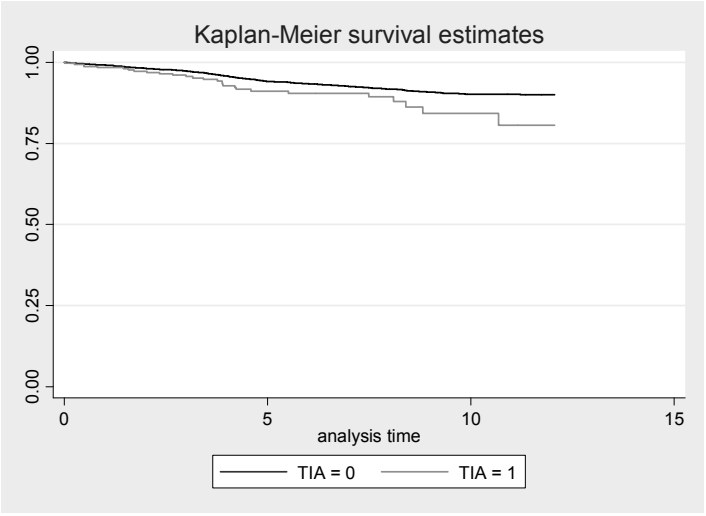

Table 2 shows the risk of incident depression associated with TIAs and stroke. TIAs were more strongly associated with depression the more stringently depression was defined: the risk of depressive symptoms and syndromes combined was 1.30 (95% CI 0.94-1.80), the risk of depressive syndromes 1.68 (95% CI 1.12-2.51), and the risk of depressive disorders 2.42 (95% CI 1.26-4.67). Like TIAs, stroke was also related to depressive syndromes (HR 1.52; 95% CI 1.01-2.27) and to depressive disorders (HR 3.35; 95% CI 1.82-6.18). The hazard ratios showed the same pattern in the subsample of persons without a history of depression at baseline. In fact, the risk of depressive disorders after TIA was as high as 2.91 (95% CI 0.96-8.81).

Additionally, we assessed the risk of incident depression related to focal, mixed and nonfocal attacks. Table 3 shows the results. Focal attacks did not increase the risk of depressive symptoms and syndromes combined (HR 1.22; 95% CI 0.86-1.74), but significantly increased the risk of depressive syndromes (HR 1.55; 95% CI 1.00-2.39), and

depressive disorders (HR 2.17; 95% CI 1.05-4.46). Mixed attacks in particular conveyed an increased risk of depressive symptoms and syndromes combined (HR 2.25; 95% CI 1.11-4.55), and depressive syndromes (HR 3.14; 95% CI 1.39-7.12). The risk estimate of mixed attacks for depressive disorders was not statistically significant (HR 2.88; 95% CI 0.68-12.3), probably as a result of the small number of cases. In contrast, nonfocal attacks were not associated with depression.

Table 2 TNAs and the risk of incident depression using Cox' proportional hazard models*

Type of attack	Depressive syndromes and symptoms (n=736)			Depressive syndromes only (n=407)			Depressive disorders only (n=103)		
	N	HR (95%CI)	p-value	N	HR (95%CI)	p-value	N	HR (95%CI)	p-value
Complete study population (n=5095)									
Focal attacks‖ (263)	34	1.22 (0.86-1.74)	.27	23	1.55 (1.00-2.39)	.05	9	2.17 (1.05-4.46)	.04
Nonfocal attacks (226)	23	1.00 (0.66-1.53)	.98	10	0.79 (0.42-1.49)	.47	2	0.50 (0.12-2.07)	.34
Mixed attacks (42)	8	2.25 (1.11-4.55)	.02	6	3.14 (1.39-7.12)	.01	2	2.88 (0.68-12.29)	.15
Any attack (458) †	59	1.18 (0.90-1.55)	.24	33	1.22 (0.85-1.77)	.28	12	1.53 (0.81-2.89)	.19
Persons without history of depression (n=3454)									
Focal attacks (170)	16	1.38 (0.83-2.30)	.22	11	1.88 (1.01-3.50)	.05	3	2.42 (0.70-8.39)	.16
Nonfocal attacks (156)	14	1.29 (0.75-2.23)	.36	6	1.06 (0.46-2.43)	.89	2	1.58 (0.37-6.81)	.54
Mixed attacks (26)	3	2.11 (0.67-6.65)	.20	3	3.70 (1.16-11.77)	.03	1	6.88 (0.90-52.70)	.06
Any attack (319) ‡	29	1.35 (0.91-1.99)	.14	16	1.45 (0.85-2.45)	.17	5	2.29 (0.84-6.22)	.11

* adjusted for age, sex, SES, ADL, history of depression, smoking, diastolic and systolic blood pressure, diabetes, history of cardiovascular disease , chronic heart failure, and use of anti-hypertensives, and censored for stroke; † otherwise known as TIA; ‡ numbers of individual types of TNAs do not add up to number of all TNAs due to persons with more than one type of TNA

Table 3 Type of attack and the risk of incident depression using Cox' proportional hazard models (n=5,095)*

	Depressive syndromes and symptoms (n=736)		Depressive syndromes only (n=407)		Depressive disorders only (n=103)	
	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
Focal attacks (n= 263) †	1.22 (0.86-1.74)	.27	1.55 (1.00-2.39)	.05	2.17 (1.05-4.46)	.04
Mixed attacks (n= 42) ‡	2.25 (1.11-4.55)	.02	3.14 (1.39-7.12)	.01	2.88 (0.68-12.3)	.15
Nonfocal attacks (n= 226) §	1.00 (0.66-1.53)	.98	0.79 (0.42-1.49)	.47	0.50 (0.12-2.07)	.34

* adjusted for age, sex, SES, ADL, history of depression, smoking, hypertension, diabetes, history of cardiovascular disease, chronic heart failure, use of anti-hypertensives, and stroke; † focal attacks are transient neurological attacks that present with focal symptoms only, ‡ mixed attacks present with focal and nonfocal symptoms, and § nonfocal attacks with nonfocal symptoms only.

Discussion

In this population-based cohort, TIAs were associated with an increased risk of incident depression. Nonfocal attacks did not increase the risk of incident depression. The risk of TIAs for depression was similar to that of stroke. Although TIAs, like stroke, are clinical indicators of long-term atherosclerotic damage to the brain and occur frequently, the risk of TIAs for depression has, to the best of our knowledge, not been studied prospectively before.

Prospective studies of vascular depression have mostly investigated the association between cerebrovascular risk factors and depression, such as smoking, blood pressure, diabetes, dyslipidemia, history of cardiovascular disease, or the use of antihypertensives. However, none of the risk factors were found to consistently predict depression (36, 37). Similarly, composite scores of these risk factors were related to incident depression in some studies but not in others (36-40). Results from prospective imaging studies that investigated a link between severity of white matter lesions with new-onset depression are more consistent, with most finding no relationship (41-44). In the study that yielded a positive association, prevalent and incident dementia had not been taken into account (45). No relationship between progression of white matter lesions and incident depressive symptoms has been found either (44).

The association between stroke and subsequent depression has been studied extensively (3, 4, 46, 47). Between 10 and 50% of patients develop depression in the first month after a stroke, and one-year post-stroke the risk is still higher than 30% (1-3). It remains unclear, however, what the direct contribution of the brain lesion is and what the contribution of reduced functional status is to the increased risk of depression. To add to the complexity, depression secondary to stroke has been associated with different locations and with decreased catecholamine activity in the injured and uninjured brain structures (2, 4, 48).

In our study, we were able to test the vascular depression hypothesis in patients with clear clinical manifestations of ischemic brain damage without concomitant permanent loss of neurological function. We showed that the risk of depression after TIA is similar to that after stroke in a population-based cohort. In a clinical study, the prevalence of major depressive disorder in patients with carotid stenosis and TIA was similar to that of patients with stroke (6). It is also known that depression can occur long after the index stroke (47), like depression after TIA in our study. Cerebrovascular accidents, irrespective of the duration of initial symptoms and loss of function, predict new-onset depression over an extended period of time. Thus, TIAs, like stroke, require immediate and extensive tests to detect underlying pathology, but similarly, also careful long-term follow-up to monitor and prevent the onset of depression.

The association of TIAs but not nonfocal attacks with depression strongly suggests a role for focal cortical brain damage. However, stroke location has not been associated with depression consistently (2, 4, 48), and imaging studies have found that damage to grey matter, white matter, and basal ganglia were all associated with depression (14). Moreover, transient global amnesia, qualified as a nonfocal attack in our study, was associated with a personal or family history of psychiatric diseases in another study (22). It is possible, that the heterogeneity of the group of nonfocal attacks in our study explains the apparent contrast with TIAs. For instance, syncope, which made up 25% of the nonfocal attacks in our study (15), tends to have multiple causes in elderly patients (49).

We found that TIAs are associated with incident depression, like stroke. This suggests that not the functional impairment but rather the atherosclerotic process underlies the depression. Yet, MRI-visualized subclinical cerebrovascular disease has not been associated with depression consistently (41-45). Moreover, we cannot rule out that the clinical event provokes depression. TIAs usually occur out of the blue and may forebode potentially life-threatening stroke. This may provoke a reactive depression (4), possibly in already vulnerable persons (50), although in the present study most depressions occurred several years after the event.

Strengths and limitations

Our study was based on a large population-based cohort and long follow-up period. Data were gathered prospectively and without prior knowledge of the research hypothesis. Participants were monitored continuously for incident depression and interviews were conducted by clinicians who used DSM-IV criteria to diagnose depressions. In addition, detailed information on the occurrence of TIAs was also collected with systematic repeated interviews and continuous monitoring of medical files. However, some TIAs may have been missed or misclassified, because the diagnoses were primarily derived from medical records. There is often disagreement, even between neurologists, about whether a given patient has had a TIA (51). In order to minimize misclassification in our study, each potential TIA was classified according to a stringent protocol by multiple raters.

To rule out that depression was already present when a TIA occurred, the dates-of-onset of the depressions needed to be precise. We used all available information from interviews, prescriptions, and medical records. Moreover, the mean time-lag between the occurrence of a TIA and the onset of depression was more than three years. Another advantage of the available information on dates-of-onset was that we could perform time-varying analyses, including TIAs that had occurred after baseline.

Finally, we minimized potential confounding by adjusting for a considerable number of socio-demographic and health related confounders. Some residual confounding may have occurred because we did not have baseline data on carotid stenosis (52).

Conclusion

TIAs increase the risk of incident depression in the elderly. The high risk for post-TIA depression, a frequently debilitating disease, justifies greater attention for this long-term psychiatric outcome in daily medical practice of patients presenting with TIA. Research is needed to clarify the effect of TIAs on the disease course and treatment response in depressed patients.

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Part IV

Discussion

Chapter 10

Discussion

Exploring the results

The aim of this thesis was to examine the association of cardiovascular and cerebrovascular disease with incident late-life depression in a population-based setting. Previous studies have often been performed in clinical populations, such as in patients with cardiac disease or primary care patients (1-5), which reduces the external validity of the results. The findings of our studies apply to the heterogeneous population of community-dwelling elderly persons. Moreover, most previous studies had cross-sectional designs. The prospective nature of our studies enabled us to examine the longitudinal association of cardiovascular and cerebrovascular disease with depression. Whether heart failure, atrial fibrillation, or transient neurological attacks relate to incident depression had not been studied before.

The studies for this thesis were embedded in the Rotterdam Study, a large ongoing cohort study (6). Since 1989, 7,983 inhabitants of Ommoord, a district of Rotterdam, have participated in it. Every four years they underwent an extensive home interview and a physical examination. Detailed information on the occurrence of cardiac disease, cerebrovascular risk factors and depression was collected continuously from the medical records. Furthermore, all drugs dispensed to the participants by pharmacies in the Ommoord region were prospectively registered. In addition, a sample of 563 participants of the Rotterdam Study underwent brain MRI-scanning in 1995-1996 as part of the Rotterdam Scan Study (7).

In order to study risk factors of incident late-life depression, we needed to identify incident depressive episodes that occurred in the study population during follow-up. Depressive episodes were categorized as mutually exclusive DSM-IV defined depressive disorders, other depressive syndromes, and clinically relevant depressive symptoms. Due to the high incidence of episodes with clinically relevant depressive symptoms and to recurrence of depressive syndromes in elderly with a history of depression, the incidence of depression was high in our elderly study population.

Vascular heart disease and late-life depression

Cross-sectional studies have shown an association of heart failure and atrial fibrillation with depression (4, 5). Although depression has been established as a risk factor for incident cardiovascular disease (8-10), it is also possible that the cross-sectional associations can (in part) be explained by heart failure and atrial fibrillation as risk factors for incident depression. Heart failure gives rise to reduced cardiac output that can lead to insufficient cerebral perfusion. Disturbances of heart rate and heart-rate variability can interrupt healthy brain function (11). Another explanation for the cross-sectional association between these cardiac disease and depression, can be that patients often use beta-blockers. These drugs are often used in heart failure and atrial fibrillation and physicians have been concerned about a depressogenic effect ever since the introduction on the market in late

60s. However, the potential bias introduced by the use of cardiovascular medication has received little attention (12-14).

We found that heart failure was associated with an increased risk of incident depressive syndromes. In participants with heart failure, the use of loop-diuretics in persons was associated with a decreased risk of depressive syndromes. Atrial fibrillation, on the other hand, did not convey an increased risk of either depressive symptoms or syndromes. To our knowledge, no studies have been published before that investigated the longitudinal relationship of these heart diseases with incident late-life depression.

We found that beta-blockers in general did not increase the risk of depressive symptoms or syndromes. However, lipophilic beta-blockers with serotonergic affinity, in our study mostly propranolol, were associated with depressive symptoms in the first three months of use. Our findings confirm previous results for propranolol from case reports and observational studies (15-17). There are however also two cohort studies and two meta-analyses of trials have yielded null findings for lipophilic beta-blockers (16, 18-20). However, lack of systematic and timely assessment of depression, sometimes resulting in very small numbers of cases, may well have contributed to insufficient power of these studies (21). Propranolol is hardly ever prescribed for cardiovascular disease, but primarily for anxiety, migraine, alcoholism, and thyroid disease.

The results of our studies suggest that loss of daily functioning is an important intermediate factor in the relation between cardiovascular disease and incident depression. Heart failure is related to loss of daily functioning, whereas uncomplicated atrial fibrillation is not. Moreover, we found that use of loop-diuretics in persons with heart failure was associated with a decreased risk of depression. Loop-diuretics can provide quick relief of the debilitating symptoms of heart failure, such as breathlessness. Other chronic disease with low quality of life such as rheumatoid arthritis and chronic obstructive pulmonary disease bear a high risk of depression as well (22). Another non-biological explanation of our findings could be that experiencing the symptoms of a (life) threatening disease, such as heart failure, may provoke a psychological reaction, and when coping mechanisms fail, a patient may become depressed. In contrast, atrial fibrillation has a far better prognosis than heart failure and thus it will not provoke such a psychological reaction easily.

Vascular brain disease and late-life depression

An abundance of cross-sectional studies has shown an association between cerebrovascular disease and depression (23, 24). These findings have been confirmed in the Rotterdam Study (25, 26). High rates of depression in cerebrovascular disease might be explained by an increased risk of cerebrovascular disease in individuals with depression, by an increased risk of depression in individuals with cerebrovascular disease, or by both. Indeed, depressive symptoms have been linked to development of atherosclerosis, incident coronary heart

disease, incident stroke and total mortality in apparently healthy elderly persons (27-30). The question remains whether cerebrovascular disease is a risk factor for depression.

In 1997, the vascular depression hypothesis was originally formulated as: "cerebrovascular disease can predispose, precipitate, or perpetuate a depressive syndrome in older adults" (31). The authors further argued that "direct testing of the vascular depression hypothesis is not possible since the mechanisms of depression are unknown". In other words, cerebrovascular disease was suggested to catalyze other depressogenic mechanisms. Indeed, it has been shown that stressful life events carry a greater risk of depression in the presence of vascular risk factors (32), and that MRI-visualized brain lesions are associated with persistence and worsening of depressive symptoms over one year (33), but more population-based studies on these topics are still lacking. The majority of prospective studies published to date, like the studies presented in this thesis, assessed whether cerebrovascular disease increased the risk of *incident* depression in the elderly. The implicit hypothesis is that atherosclerotic brain disease has a distinct etiological role in late-life depression (34). A variety of risk factors has been investigated, ranging from individual cerebrovascular risk factors, composite scores of these risk factors, extra cerebrovascular damage, MRI visualized brain damage to clinical cerebrovascular disease. The results of the studies in this thesis and other population-based studies are discussed below.

In our study about cerebrovascular risk factors, smoking and the use of antihypertensive drugs were the only individual risk factors related to incident depressive symptoms, and diabetes the only one associated with incident depressive syndromes. All other individual risk factors, i.e. cholesterol, diastolic and systolic blood pressure, a history of cardiovascular disease, atrial fibrillation, left ventricular hypertrophy, or the use of statins and anticoagulants were not related to either incident depressive symptoms or syndromes. Apart from an ischemic effect on cerebral small vessels, smoking, diabetes and anti-hypertensive drugs have also been hypothesized to cause abnormalities in neurotransmitter metabolism. Moreover, the association between diabetes and depressive disorders may be explained by obesity, a risk factor for diabetes and depression (35), for which we did not adjust. Other population-based studies about cerebrovascular risk factors have yielded similar results (32, 36-44). The only exceptions were that serum total cholesterol, HDL cholesterol, diabetes and history of heart disease were found to be associated with incident depression after two years of follow-up (36, 38). However, the effects of these risk factors were estimate in models that were unadjusted for other risk factors, such as smoking and obesity.

With respect to composite score of vascular risk factors, we found that the Framingham stroke risk score predicted depressive disorders, but not depressive symptoms. As the Framingham stroke risk score was developed to identify persons at substantially increased stroke risk resulting from their vascular risk profile (45), this finding seems to support the 'vascular depression' hypothesis. However, the score includes diabetes and heart failure that may be associated with incident depressive disorders not just through cerebrovascular

mechanisms such as stroke, as mentioned before. Other population-based studies found no relationship with cumulative scores for vascular burden (32, 46).

Two studies assessed the risk that extra cerebral damage on the risk of incident depression. We found that diminished retinal microcirculation, whether indicated by smaller arteriolar or larger venular calibers, was not associated with incident depressive symptoms or syndromes. Aterosclerosis in terms of carotid plaques, aortic calcifications, peripheral arterial disease, intima-media thickness of the right and left common carotid artery, a composite measure of these four measures, and finally coronary calcification were also not predictive of incident depressive symptoms or incident depressive syndromes (47).

White matter lesions have always been at the heart of the vascular depression hypothesis (34, 48, 49). In our MR-imaging study, however, there was no association between baseline volume of white matter lesions and incident depressive symptoms or syndromes (50). Moreover, similar results were yielded by a study in an American general population (33). In a French general population, on the hand, higher baseline volume of white matter lesions was related to a higher the risk of developing depressive symptoms during a follow-up of four years (51). An important difference with the two other before mentioned studies was, however, that prevalent and incident dementia had not been taken into account. No relationship between progression of white matter lesions and incident depressive symptoms has been found either (52). Another remarkable finding of our imaging study was that brain infarcts were not associated with incident depressive symptoms or syndromes (50). Around 85% of these infarct consisted of so-called silent, or unrecognized, strokes (53). Other structural brain changes, such as cortical atrophy, and hippocampal and amygdalar volumes have not been related to incident depressive symptoms or syndromes in the Rotterdam Scan Study either (50, 54).

Stroke and transient neurological attacks represent clearly recognizable clinical manifestations of long-term atherosclerotic damage to the brain. In our study of transient neurological attacks, we found that focal attacks and mixed attacks were associated with an increased risk of incident depressive syndromes and disorders. Nonfocal attacks were not related to depression. A meta-analysis showed that one third of stroke patients developed depression in the year following the stroke (55). In a clinical study, patients with transient ischemic attacks had significantly less severe depressive symptoms than stroke patients measured one year after the attack (56).

Overall, the studies in this thesis and those from other population-based settings show that individual cerebrovascular risk factors, composite scores of these risk factors, extra cerebral aterosclerosis, changes in retinal microcirculation, and MRI visualized brain damage are not related to incident depression. Only clinical cerebrovascular diseases, such as strokes and transient neurological attacks, seem to be associated with incident depression (24, 55). This is more compatible with a psychological than with a biological role of cerebrovascular disease in the etiology of *incident* late-life depression. Stroke and tran-

sient cerebrovascular attacks usually occur out of the blue and may forebode potentially life-threatening re-occurrences. Patients might experience them as a sword of Damocles hovering over their head. Alternatively, functional consequences of cerebrovascular disease may be the causal pathway by which vascular brain lesions are associated with depressive symptomatology. In a meta-analysis, besides stroke severity, physical disability and cognitive impairment were risk factors for post-stroke depression (55).

Where do all these results leave us? The lack of an association of unsymptomatic cerebrovascular disease and risk factors with the occurrence of new depression suggests that vascular changes observed at the time of the initial assessment have exerted their effect on mood by that time (33). Clearly, longitudinal studies are needed to examine the relationship between incident vascular disease and depression so that the time course can be examined more precisely. In addition, the observation that individuals with unsymptomatic cerebrovascular disease who were not depressed at baseline did not tend to become depressed during follow-up raises the question whether they may have protective factors (biological, psychological, or social) that insulate them from depression. Future studies should address this possibility.

Methodological issues

Causal inference of results from observational studies requires reliable and valid results. Reliability, or repeatability, requires sufficient power, and validity requires lack of bias. Below, I will discuss how we tried to optimize reliability and validity of the studies presented in this thesis.

Reliability

A study's reliability depends primarily on its power, given that in an epidemiological study the possibility of a false-positive finding is usually a priori set to 5% given a priori formulated hypotheses. Power of an epidemiological study depends on the size of the effect that is examined, the number of cases in the exposed and unexposed group, and the precision with which the outcome is measured. Sample size was already determined at the offset of the studies in this thesis. The validity (sensitivity and specificity) and reliability of the tests that were used to establish the cases, is discussed below.

Identifying incident episodes of depression has been a particular challenge. Unlike for instance schizophrenia or dementia, depression is a remitting and often recurring disease. In other words, it is not a disease that once it has occurred will not go away and can be identified even long after it has occurred. Most prospective studies that have been published previously were based on sequential examinations rounds. An example of this design is our study on cerebrovascular risk factors. At baseline and during the follow-up

rounds, participants were screened by trained interviewers with the CES-D, which has been validated in elderly populations, and has a sensitivity of 100% and specificity of 88% using a cut-off of 16 (57). Subsequently, experienced and carefully trained clinicians interviewed screen-positive participants with the Present State Examination (58). However, when depressive episodes are identified during sequential examination rounds only, episodes that have developed and remitted in the interval between rounds may be missed. This will occur especially if the periods between rounds are long, relative to the median duration of episodes.

In order to enhance the number of incident depressions identified, information was collected with additional assessment methods. The self-reported history of depression, solicited during the visits, included standardized questions to ascertain whether and when participants had had a depressive episode, and if they had been treated. However, episodes will still be missed, because people tend to forget or undervalue past depressive episodes, particularly if they occurred more than 5 years ago (59). Even episodes of depression for which they received inpatients are sometimes forgotten. The longer the periods between assessments are relative to people's memory, the more episodes will remain undetected.

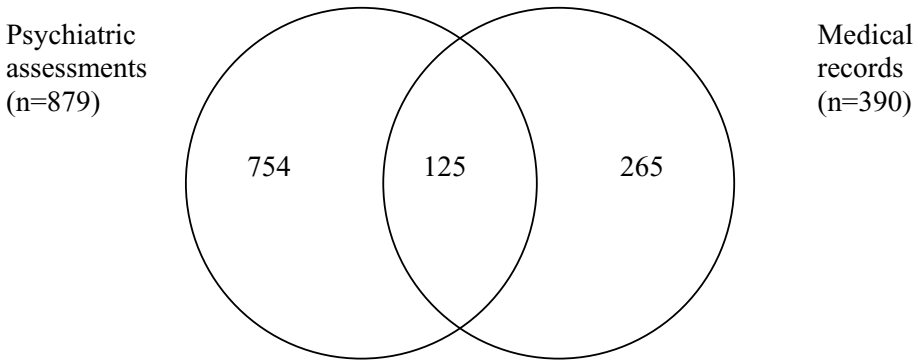
We also used continuous monitoring of medical records to identify depressions. Trained research-assistants scrutinized the medical records of the general practitioners (GPs) and copied the information about a potential depression using a list of predefined cue words. Two research physicians independently assessed this information according to a predefined protocol, and discussed discordant assessments. Continuous surveillance of medical records is seldom used in psychiatric epidemiology. Underdetection of psychiatric diseases in daily medical practice, record keeping by physicians and retrieving the information from those records may all be imperfect. General practitioners diagnose between 30 to 60% of depression, with lower recognition for milder cases (60-62). However, when a general practitioner diagnoses a depression, this most probably reflects actual depressions (63). Moreover, the reports from mental health professionals to the GPs were often elaborate, and substantiated the DSM-classified diagnoses.

The last source of information consisted of the automatic and digitalized registration of all antidepressants dispensed to the participants to identify incident depressions. The pharmaceutical records have high reliability and the information from the records is particularly useful to specify the date-of-onset of episodes. However, modern antidepressants are commonly prescribed for other indications such as anxiety disorders, sleeping disorders, migraine, or neuropathic pain (64, 65). Population surveys and family practices studies have shown that 43-56% of patients receiving an antidepressant do not fulfill the criteria of depression (64, 66-68).

The main rationale for using data from other sources, albeit with different diagnostic certainty and reliability, was to ensure that detection of (incident and recurrent) depressions was as high as possible. Increasing the number of cases increases the power of a study.

Power is also enhanced by establishing specific DSM-IV defined diagnoses. In most other population-based studies, cases have been defined as a score above a pre-specified cut-off on a screening instrument for depressive symptoms, mostly the CES-D, or as indicated by the use of anti-depressant medication (18, 19, 33, 51). Both CES-D and anti-depressant drug use have low specificity with only around 20% of screen-positives and 50% of users of anti-depressant medication having in fact a DSM-defined depression (44, 57, 64, 66-68). (An illustration of loss of power as a result of error in the assessment of depression is provided in our study about heart failure: even though the total number of cases of depressive symptoms and syndromes combined (any depression) is almost twice as high as the number of depressive syndromes only, the confidence intervals are wider.) In our study, the mental status of CES-D screen-positives was further assessed in a psychiatric interview, as explained before. A great advantage of this method is that it provides accurate DSM-IV defined diagnoses. To take into account the lower levels of diagnostic certainty from the medical records, we categorized the information on depressive episodes conservatively. Moreover, we regarded antidepressant use without a verified diagnosis from one of the other sources as a marker of depressive symptoms in the incidence study, but not in the other studies presented in this thesis.

Figure 1 Distribution of depressions identified from psychiatric assessments and medical records



What can be learned from our experience with identifying new occurrence of depression? As depicted in figure 1, the psychiatric assessments contributed more than the monitoring of medical records to the number of identified depressions. Moreover, the most sensitive and specific of the assessments methods that we used was the two-step procedure with CES-D and psychiatric interview in screen-positives during examination rounds. Perhaps it would have been more efficient to administer this assessment more frequently than every four to five years instead of continuously monitoring medical files. As late-life depression recovers in 60% of patients in one year and in 70-80% in two years, an assessment

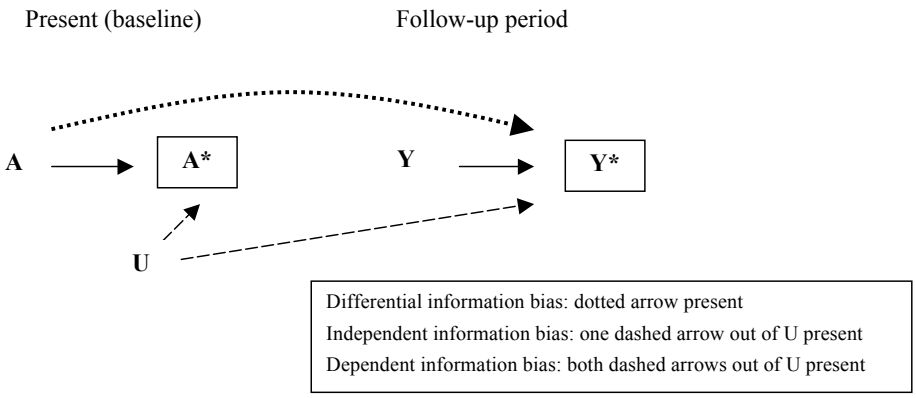
every two years would probably have been sufficient (69-76). A self-report CES-D or a 10-item CES-D could have been used for relatively quick and inexpensive screening in the interval between examination rounds. To determine the history of depression, a validated questionnaire or interview method administered during home interviews by trained interviewers could have been used.

Validity

As mentioned before, the major threats to the validity of observational studies are confounding, information bias, and selection bias. Causal diagrams may facilitate discussions about the presence of bias in epidemiological studies (see figure 2-4). In a causal diagram, the assumed causal relationships between exposure (A), outcome (Y) and other variables of interest can be schematically illustrated (77, 78). Nodes are used to depict the variables and arrows the causal effect of one node on another. Variables that merely mediate are usually omitted from the diagram. As causes precede their effects, the diagrams are acyclic: one can never start from one variable and, following the direction of the arrows, end up at the same variable (78).

Information bias, or measurement bias, is traditionally described as bias resulting from error in the measurement of the exposure and disease status. To illustrate information bias in a causal diagram, additional nodes are required: A* for measured exposure, Y* for measured outcome, and node U for unmeasured variable(s). Figure 2 presents the three mechanisms by which measurement error may give rise to information bias in a prospective study (ref).

Figure 2 Information bias in prospective studies



A stands for true exposure status, A* for measured exposure status, Y for true outcome status, Y* for measured exposure status, and U for unmeasured variables. Boxes around nodes indicate that the variables that are controlled for in the analysis.

To decrease error in the measurement of the exposure in the studies of this thesis, detailed data was collected about cardiovascular and cerebrovascular disease. Again, data from the examination rounds and medical files were used to establish cases of cardiac and cerebrovascular disease. For the imaging study, an MRI was made in a subgroup of more than 500 participants. The relevance of accurate information on exposure is that information bias (and confounding) is reduced.

Although the information on exposure and outcome were collected independently of each other, by different groups of researchers, some differential information bias might still have occurred. If persons with heart failure or transient neurological attack visited their GP or cardiologist more frequently, this will increase the probability that depressions were identified. Thus, analyzing these exposures as time varying variables, like we did, may reduce independent nondifferential information bias on the one hand, but induce some differential information bias on the other. However, given the mean time-lag of more than three years between these diseases and depression, the bias is probably small. Similar differential bias could have occurred in our study about beta-blockers, because physicians have been shown before to err in the direction of falsely calling beta-blocker users cases than users of other drugs (18).

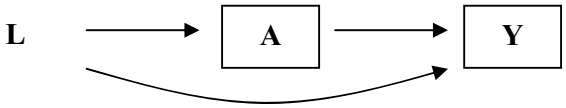
Confounding occurs when a common cause of the exposure and outcome is not controlled for, even if the exposure has no causal effect on the outcome (see figure 3) (78, 79). This is shown in figure 3 by the presence of the so-called backdoor path (or association) from A through L to Y, independent of an arrow between A and Y.

In the studies of this thesis, confounding was minimized by adjusting for factors that were assumed to be common causes of cardio- or cerebrovascular disease as well as depression according to content knowledge. An abundance of information on socio-demographic and health related factors is available in the Rotterdam Study. If the number of baseline confounders was relatively high, the factors that hardly changed the risk estimate were sometimes not included in the analysis in order to preserve power. In addition, given that depression is a risk factor for vascular disease (ref), we rerun the analyses in the subsamples of persons without a history of depression. We also used the time-varying information that was available about the occurrence of confounders such as diabetes and myocardial infarction. Thus, we were able to extensively adjust for confounding.

Some residual confounding may still have occurred. We lacked data on thyroid disease related to atrial fibrillation, on severity of heart failure in users of loop-diuretics (we did not have information on New York Heart Association (NYHA classes I-IV), or cholesterol levels when studying transient neurological attacks. Moreover, in pharmaco-epidemiological studies confounding by indication may occur. Propranolol, the most commonly used high lipid-soluble beta-blocker, is often prescribed for symptoms that are closely related to depression such as anxiety, alcoholism, and thyroid disease. Finally, overadjustment

may have occurred. In the study on cerebrovascular risk factors, we made one model that included all factors, while some factors are not confounders of others. In order to avoid overadjustment in the Cox' regression models of the other studies, we adjusted for confounders that are also intermediates by only taking their baseline status into account.

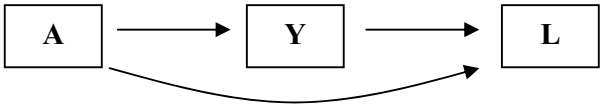
Figure 3 Confounding



A stands for exposure, Y for outcome, and L for common causes of A and Y, i.e. potential confounder(s) that should be controlled for. Boxes around nodes indicate that the variables that are controlled for in the analysis.

Selection bias occurs when a common effect of the exposure and the outcome is adjusted for in the design or analysis (see figure 4) (80). The box around the common effect in figure 4 depicts that it is adjusted for.

Figure 4 Selection bias



A stands for exposure, Y for outcome, and L for common effects of A and Y which should *not* be controlled for in the study. Boxes around nodes indicate that the variables that are controlled for in the analysis.

A major advantage of using multiple sources to identify depression, like we did, is that selection bias is reduced. Depressions in participants who are lost to follow-up are less easily missed. In the study about cerebrovascular risk factors, for instance, the probability that a participant drops out is higher if he has more vascular health problems at baseline and if he is depressed at the time of the follow-up measurement (the common effect being participation in follow-up round). This could have lead to underestimation of the true risk. (When we later rerun the analysis on our data set with incident cases from multiple sources, it yielded similar results.)

A potential source of selection bias might have occurred as a result of censoring for death, because depression in patients with heart or brain disease is often related to higher mortality. If patients with heart or brain disease died before their depression was diagnosed and recorded, risks will be underestimated. The higher baseline age of the study population and thereby the death rate, the larger this selection bias may be (81). In our dataset, for instance, stroke has a protective effect on incident depression. This is however

implausible, given the abundance of literature showing that stroke actually carries a high risk of depression (55). Consequently, adjusting for intermediate (time-varying) stroke has possibly led to overestimation of the true risk of transient neurological attacks.

Recommendation: from associations to causal effects

Currently, progression of longitudinal epidemiological studies is primarily sought by extending data collection. More and more advanced techniques are used to measure more exposure and outcomes, and measure them more accurately. In addition, large population-based cohorts are observed over long periods. The Rotterdam Study, from which the data for this thesis have been drawn, is an example of this practice. Unmistakably, these initiatives have greatly expanded epidemiological knowledge. However, in many of these longitudinal studies conventional statistical methods to control for bias are used, such as matching and regression analyses (82, 83). These methods do not allow causal inference of the associations that have been examined, because adjustment for common causes that are also common effects of exposure and outcome introduces selection bias. New methods to control for bias should be used.

As the most realistic interventions often take place over time, statistical methods that appropriately handle time-varying exposures and adjust for time-varying confounders to estimate their causal effect are required. Marginal structural models make use of inverse probability weighting to appropriately adjust for measured time-varying confounders affected by prior exposure (84, 85). For example, myocardial infarction can precede the use of beta-blockers and the occurrence of depression, but the use of beta-blockers diminishes the risk of recurrent myocardial infarction. Conventionally, time-varying confounders are adjusted for by adding them in the regression or survival model, but this yields the partial effect of the exposure on the outcome only. Moreover, selection bias can be introduced when the confounder is also a common effect. Although the assumption of no residual confounding is hard to check, marginal structural models have been shown to yield risk estimates comparable to those found in randomized controlled trials (84, 86). In some instances, an instrumental variable analysis could be used to diminish bias. Mendelian randomization makes use of genetic variants as a randomizer (instrumental variable) to estimate unbiased associations in observational studies (87, 88). The analysis requires the identification of a genetic variant that robustly predicts the exposure of interest, and does not predict the outcome except through this exposure (88). For instance, the association between obesity and depression may be estimated using genes that predict body mass index or waist circumference.

Finally, some recommendations may be made that relate to daily medical practice. We found that heart failure and transient neurological attacks were associated with an

increased risk of incident depression. There was no association between atrial fibrillation, structural brain changes (brain atrophy, brain infarcts and white matter lesions) or diminished retinal microcirculation and incident depression. Physicians should take into account the role of heart failure and transient neurological attacks in depressed patients. In non-depressed patients, treating these conditions as effectively as possible in order to optimize physical health, might possibly also prevent depression. Our findings require further if the goal is to inform public health policy or medical practice. Often we do not know the actual procedure by which each subject achieved the exposure of interest, such as a cardiac condition (89). Therefore, an observed difference in risk between exposed and unexposed participants cannot be translated into a well-defined causal effect. Studies are needed that focus on the effect that modifiable lifestyle behaviors, such as exercise and smoking, have on depression. All analytic methods for causal inference from observational data (stratification/regression, matching, inverse probability weighting, instrumental variable methods) yield effect estimates that are only as well defined as the interventions that are being compared.

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Chapter 11

Summary/ Samenvatting

Summary

Depression occurs frequently. Almost one out of five persons develops a depression at least once in his lifetime. Besides genetic predisposition, several external risk factors, such as traumatic life events, poverty, female sex, and somatic diseases. The aim of the studies presented in this thesis was to assess the longitudinal relationship between vascular heart and brain disease and the risk of new-onset depression. The studiew were embedded in the Rotterdam Study. This a prospective study among 7983 inhabitans of Ommoord, a district of Rotterdam. At the start of the study in 1989 they were 55 years or older. During 4-yearly examination rounds, they were interviewed and received multiple tests to establish their health status. Health related factors that could influence the relationship between vascular diseases and depression, and that could bias the results of the studies were measured as well.

We used several sources to identify participants with a depression. Since 1993 participants are screened with questionnaire for depressive symptoms during examination rounds. Since 1997, screen-positive persons are invited to participate in a psychiatric interview. Additionally, medical files of general practitioners were continuously monitored and pharmacies provided online information on the use of anti-depressant medication. We also used the self-reported histories of depression to identify depressions that had occurred before the start of the study and in-between examination rounds. We categorized the depressions as depressive syndromes, including DSM-IV defined major depression, or clinically relevant depressive symptoms. In our study among more than 5000 elderly persons new-onset depressions occurred frequently (chapter 2). This was due to the high incidence of episodes with clinically relevant depressive symptoms and to recurrence of depressive syndromes in elderly with a history of depression.

Subsequently, we studied the association between vascular heart diseases and depression and the role of cardiovascular medication in this association. Heart failure is a condition in which a problem with the structure or function of the heart impairs its ability to supply sufficient blood flow to meet the body's needs. In our study, heart failure was not associated with depressive symptoms, but it was associated with an increased risk of incident depressive syndormes (chapter 3). We also found that use of loop-diuretics, which can provide quick relief of breathlessness and swollen ankles, was associated with a decreased risk of depression. There was no association between atrial fibrillation and late-life depression. We also studied the risk of depression as a result of atrial fibrillation, the most common cardiac arrythmia. When we took differences in age and gender between people with and without atrial fibrillation into account, atrial fibrillation seemed associated with an increased risk of depression (chapter 4). However, this association disappeared when we adjusted for differences in health status.

Beta-blockers are often used for various cardiovascular diseases, such as hypertension, myocardial infarction, heart failure, and atrial fibrillation. Our study showed that use of beta-blockers in general is not associated with depression (chapter 5). However, in the first three months of use, beta-blockers with high lipi-solubility, that penetrate the brain relatively easily, are associated with depressive symptoms. In our studypopulation, this consisted mostly of propranolol, a beta-blocker usually prescribed for anxiety disorders, alcoholism, or thyroid disease. Given the association of these diseases with depression, could explain the association of propranolol with depressive symptoms.

Next, we studied the association between cerebrovascular risk factors and diseases and new-onset depression. This builds on international studies about the 'vascular depression hypothesis' that proposes that vascular damage to the brain predisposes to late-life depression. First, we studied wether risk factors for cerebrovascular disease are associated with depression. We found that smoking, and the use of antihypertensive drugs, diabetes and the Framingham stroke risk score, a composite score indicating the risk of stroke, were associated with depression (chapter 6). The other risk factors, that is high serum cholesterol, blood pressure, history of cardiovascular disease, atrial fibrillation, and the use of statins and anticoagulants, were not related to depression.

In addition, we studied more direct measures of vascular brain damage. The volume of retinal vessels reflect the status of brain vessels. In our study, there was however no association between this measure and new-onset depression (chapter 7). Vascular damage to the brain can also be measured on MRI-scan in terms of the volume of grey and white matter, and the presence of infarcts. In a subsample of our study population such scans have been made. Again, we did not find an association: the volume of grey and white matter, nor infarcts were related to developing depression (chapter 8). Finally, we studied the risk of depression after a transient neurological attack (TIA). This is a clinical indicator of long-term atherosclerotic damage to the brain. TIAs, like stroke, conveyed an increased risk of depression (chapter 9).

We conclude that vascular heart and brain disease with severe or life-threatening symptoms, such as heart failure and TIAs, increase the risk of depression. Despite many studies showing a cross-sectional associations between subclinical cardio- and cerebrovascular disease and depression, we did not find a longitudinal association in our study. Possibly, loss of daily functioning and psychological effects of vascular heart and brain disease have a greater effect on the riks of new-onset late-life depression, than the vascular damage itself. We close with the recommendation to use statistical randomisation techniques in future epidemiological cohort studies to minimize bias.

Samenvatting

Depressie is een veel voorkomende aandoening. Ongeveer 15-20% van de mensen ontwikkelt tenminste één keer in zijn leven een depressie. Behalve een vermoedelijke genetische aanleg, bestaan er verscheidene externe risicofactoren, zoals traumatische gebeurtenissen, armoede, vrouwelijk geslacht en lichamelijke ziekten. Het doel van het onderzoek in dit proefschrift was de longitudinale relatie tussen vaatziekten van hart en hersenen en de ontwikkeling van depressie bij oudere mensen te onderzoeken (hoofdstuk 1). Het onderzoek maakte deel uit van het Erasmus Rotterdam Gezondheid Onderzoek (ERGO), internationaal bekend als 'the Rotterdam Study'. Dit is een prospectief onderzoek waaraan 7983 inwoners van de wijk Ommoord in Rotterdam deelnamen. Bij de start van de studie in 1989 waren zij 55 jaar of ouder. Tijdens 4-jaarlijkse onderzoeksronden werden zij geïnterviewd en werd een lichamelijk onderzoek verricht om hun gezondheidstoestand te bepalen. Gezondheidsfactoren die de relatie tussen vasculaire ziekten en depressie kunnen beïnvloeden en de resultaten van het onderzoeken zouden kunnen vertekenen werden ook gemeten.

Wij gebruikten verschillende bronnen om deelnemers met een depressie te identificeren (hoofdstuk 2). Sinds 1993 worden de deelnemers tijdens de onderzoeksronden met een vragenlijst gescreend op depressieve symptomen, en sinds 1997 is daar een psychiatrisch interview aan toegevoegd voor de mensen die veel depressieve klachten rapporteerden tijdens de screening. Verder gebruikten wij medische dossiers van huisartsen inclusief de daarin aanwezige correspondentie van specialisten, en ook informatie van apotheken over het gebruik van antidepressiva. Daarnaast werd de medische voorgeschiedenis van de deelnemers uitgevraagd tijdens de onderzoeksronden om depressies voor het begin van de studie en depressies tussen de onderzoeksronden in vast te stellen. Wij onderscheiden episoden met depressieve klachten van depressieve syndromen, die ofwel voldeden aan de daarvoor algemeen geldende criteria (DSM-IV) of door een arts of een psycholoog waren gediagnosticeerd. In ons onderzoek bij meer dan 5000 oudere mensen traden vaak nieuwe depressieve episoden op (hoofdstuk 2). Dit bleek te zijn toe te rekenen aan episoden van depressieve symptomen en aan terugkerende depressies bij ouderen met een voorgeschiedenis van depressie.

Vervolgens onderzochten we de associatie tussen verschillende cardiovasculaire ziekten en depressie en de rol van cardiovasculaire medicatie in deze relatie. Hartfalen treedt op als het hart als gevolg van een hartaandoening niet meer in staat is de hoeveelheid bloed rond te pompen die het lichaam vraagt. Hartfalen was in ons onderzoek niet geassocieerd met het ontwikkelen van depressieve symptomen, maar wel met het ontwikkelen van depressieve syndromen (hoofdstuk 3). Patiënten met hartfalen gebruiken vaak lisdiuretica, waardoor de klachten van benauwdheid en gezwollen enkels in korte tijd kunnen verminderen. De patiënten die deze medicijnen gebruikten hadden een verlaagd risico op depressieve syndromen. Ook hebben we het risico op depressie onderzocht als gevolg van boezemfibril-

leren, een veel voorkomende hartritmestoornis. Als alleen rekening gehouden werd met verschillen in geslacht en leeftijd tussen de mensen met en zonder boezemfibrilleren leek een verhoogd risico op depressie te bestaan (hoofdstuk 4). Dit verband bleek echter niet meer aanwezig te zijn als ook rekening gehouden werd met verschillen in gezondheidstoestand.

Beta-blokkers worden vaak gebruikt bij allerlei hart- en vaatziekten, waaronder hoge bloeddruk, hartaanval, hartfalen, en boezemfibrilleren. Ons onderzoek toonde aan dat gebruik van beta-blokkers in het algemeen niet geassocieerd was met depressie (hoofdstuk 5). Echter, in de eerste drie maanden van gebruik waren beta-blokkers met een hoge vetoplosbaarheid, die relatief gemakkelijk in de hersenen kunnen binnendringen, wel geassocieerd met depressieve symptomen. In onze onderzoekspopulatie betreft dat meestal propranolol, een middel dat meestal gegeven wordt bij angststoornissen, alcoholisme of schildklieraandoeningen. Aangezien deze ziekten vaak geassocieerd zijn met depressie, is het de vraag of propranolol een eigenstandig effect heeft op het risico van depressie.

Tevens hebben wij de associatie tussen cerebrovasculaire ziekten en depressie onderzocht. Dit sluit aan bij het internationale onderzoek naar de 'vasculaire depressie' hypothese die stelt dat depressies bij ouderen eerder optreden als sprake is van cumulatieve vasculaire schade aan het brein. Eerst hebben wij onderzocht of factoren die het risico op vasculaire hersenziekten verhogen geassocieerd zijn met depressie (hoofdstuk 6). Wij vonden dat roken, het gebruik van een medicijn tegen hoge bloeddruk, diabetes en de *Framingham stroke risk score*, een risicomaat voor de kans op herseninfarct, geassocieerd waren met het ontwikkelen van depressie. Alle andere factoren, zoals hoge bloeddruk, verhoogd cholesterol, een voorgeschiedenis van vaatziekten van het hart, boezemfibrilleren, of gebruik van cholesterolverlagende of bloedverdunnende medicijnen waren niet geassocieerd met depressie. Vervolgens onderzochten wij meer directe maten voor vaatschade aan het brein. Het volume van de (slag)aders van het netvlies weerspiegelen de toestand van de hersenvaten. In ons onderzoek was er echter geen relatie tussen deze maat en het ontwikkelen van depressie (hoofdstuk 7). De toestand van de hersenen kan ook gemeten worden met een MRI-scan. Het volume van de grijze en witte stof, als mede de aanwezigheid van herseninfarcten, vormen een maat voor de vaatschade. In een deel van de onderzoekspopulatie was een dergelijke scan gemaakt. Opnieuw vonden wij geen verband: het volume van de grijze en witte stof, noch herseninfarcten waren geassocieerd met het ontwikkelen van depressie (hoofdstuk 8). Tot slot, onderzochten wij het risico op depressie na een *transient ischemic attack*, ook wel TIA. TIAs kunnen optreden als gevolg van langdurige vaatschade van de hersenen. TIAs bleken net als hersenberoertes gepaard te gaan met een verhoogd risico op depressie (hoofdstuk 9).

Wij concluderen dat vaatziekten aan hart en hersenen die gepaard gaan met ernstige of bedreigende symptomen zoals hartfalen en TIAs het risico op depressie verhogen (hoofdstuk 10). Ondanks dat in het verleden in dwarsdoorsnede onderzoek vaak een verband gevonden werd met vaatziekten aan hart en hersenen, vonden wij in ons longitudinale onderzoek

geen verband tussen vasculaire risicofactoren of ziekten *zonder* duidelijke symptomen en het ontwikkelen van depressie. Mogelijk spelen fysieke beperkingen en psychologische gevolgen van vasculaire ziekten aan hart en hersenen een belangrijkere rol in het ontwikkelen van depressie, dan feitelijke vaatschade aan de hersenen. Ten slotte bevelen wij aan om voor nader onderzoek vaker gebruik te maken van statistische technieken om te randomiseren, om zodoende de kans op vertekening van de resultaten nog verder te verminderen.

Dankwoord

Aan het begin mijn promotie-onderzoek zei ik vaak: “De Rotterdam Study is een rijdende trein die velen naar hun bestemming heeft gebracht. Ik heb er het volste vertrouwen in dat die trein mij daar ook zal brengen.” Nu dat zover is, wil ik de vele mensen bedanken die met hun doorlopende inzet de treinreis mogelijk maakten.

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List of publications

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KG Brühl, HJ Luijendijk, MT Muller. Nurses' and nursing assistants' recognition of depression in elderly who depend on long-term care. Journal of the American Medical Directors Association 2007; 8: 441–445.

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K Hek, CL Mulder, HJ Luijendijk, CM van Duijn, A Hofman, AG Uitterlinden, H Tiemeier. The PCLO gene and depressive disorders: replication in a population-based study. Human Molecular Genetics (in press)

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HJ Luijendijk, H Tiemeier, JF van den Berg, GS Bleumink, A Hofman, BHCh Stricker. Heart failure and incident depression in the elderly (submitted)

HJ Luijendijk, J Heeringa, A Hofman, JCM Witteman, BHCh Stricker, H Tiemeier. Atrial fibrillation and the risk of incident depression in the elderly (submitted)

HJ Luijendijk, JF van den Berg, A Hofman, H Tiemeier, BHCh Stricker. Beta-blockers and the risk of incident depression (submitted)

HJ Luijendijk, BHCh Stricker, RG Wieberdink, PJ Koudstaal, A Hofman, MMB Breteler, Henning Tiemeier. Transient ischemic attacks and the risk of developing depression (submitted)

RS Newson, K Hek, HJ Luijendijk, A Hofman, JCM Witteman, H Tiemeier. Atherosclerosis and incident depression in late life (submitted)

T den Heijer, H Tiemeier, HJ Luijendijk, A Hofman, MMB Breteler. Hippocampal and amygdalar volumes and incident depression in late life (to be submitted)

HJ Luijendijk, BHCh Stricker, H Tiemeier. Cerebrovascular disease and incident late-life depression: a review of prospective studies (to be submitted)

Other publications

HJ Luijendijk and AJB Verkaaik (red). Handboek Sociale Geriatrie. Utrecht: de Tijdstroom, 2006.

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About the author

Dika Luijendijk was born on August 18th, 1971. Following graduation from secondary school (Gymnasium-B) at Christelijk Lyceum in Zeist, her career has revolved around geriatrics, psychiatry and epidemiological research. She studied medicine at Maastricht University and received her medical degree 'met genoegen' (1999). From 2000 onward, she has practiced medicine in the department of geriatric psychiatry of BAVO-Europoort/ Parnassia BAVO Groep. She was trained as a psychogeriatrician (sociaal geriater), receiving formal education at Gerion of the Free University Amsterdam (2003). She co-edited 'Handboek Sociale Geriatrie' (2006).

Dika became interested in epidemiological research when she was a student interviewing participants for studies about depression and dementia. Stichting VSB fonds awarded her a grant to follow a Master of Public Health at the Nuffield Institute of Health in Leeds, United Kingdom (1996). Afterward, she worked as a policy-maker reporting to the committee Ontwikkelingsgeneeskunde at the Ziekenfondsraad (now programma DoelmatigheidsOnderzoek at ZonMw), and as a researcher performing a study about ageism in medical decision making at the Department of Social Medicine of Erasmus Medical Center Rotterdam. In 2003 she started the research presented in this thesis at the Department of Epidemiology of Erasmus Medical Center Rotterdam. She has been a visiting scholar of the Harvard School of Public Health in Boston, United Stated, studying the principles of causal inference in epidemiology (2007).

Dika Luijendijk is married to Xander Koolman. They have two sons: Zian and Feder.