

VASCULAR HEART AND BRAIN DISEASE AND INCIDENT LATE-LIFE DEPRESSION

H.J. Luijendijk

2010

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Vascular Heart and Brain Disease and Incident Late-life Depression

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Contents

Manuscripts based on the studies described in this thesis	6
PART I Introduction	7
Chapter 1 Introduction	9
Chapter 2 Incidence and recurrence of late-life depression	15
PART II Vascular heart disease and late-life depression	33
Chapter 3 Heart failure and loop diuretics	35
Chapter 4 Atrial fibrillation	49
Chapter 5 Beta-blockers	57
PART III Vascular brain disease and late-life depression	69
Chapter 6 Cerebrovascular risk factors	71
Chapter 7 Retinal vascular calibers	87
Chapter 8 MRI-markers of vascular brain disease	95
Chapter 9 Transient ischemic attacks	105
PART IV Discussion	119
Chapter 10 Discussion	121
Chapter 11 Summary/ Samenvatting	139
Dankwoord	145
List of publications	147
About the author	149

Manuscripts based on the studies described in this thesis

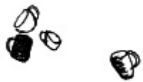
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- Chapter 6: HJ Luijendijk, BHCh Stricker, A Hofman, JCM Witteman, H Tiemeier. Cerebrovascular risk factors and incident depression in community-dwelling elderly. *Acta Psychiatrica Scandinavica* 2008; 118(2):139-48.
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- Chapter 9: HJ Luijendijk, BHCh Stricker, RG Wieberdink, PJ Koudstaal, A Hofman, MMB Breteler, H Tiemeier. Transient ischemic attacks and the risk of developing depression (submitted)
- Chapter 10: HJ Luijendijk, BHCh Stricker, H Tiemeier. Cerebrovascular disease and incident late-life depression: a review of population-based studies (to be submitted)

Part I

Introduction

Chapter 1

Introduction



1. **Characteristics of late-life depression**

2.

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

6. Compared to depression in middle age, late-life depression has some specific character-
7. istics. Depressive syndromes that escape the strict criteria of the Diagnostic and Statistical
8. Manual of Psychiatric Disorders (DSM) for major depressive disorder and dysthymia are
9. more common in the elderly (3-5). Many elderly have only some symptoms of depression.
10. Such subthreshold depressive syndromes are considered clinically relevant, because they
11. are related to increased disability and mortality, as are depressive disorders that meet DSM
12. criteria (6-10). Moreover, depression is more common in the old age than in midlife. The
13. prevalence ranges from 9 to 18 % in the general elderly population, to more than 30% in
14. long-term care residents (3, 5, 11, 12). Depression in late life often has a chronic course (3,
15. 5, 11, 13) Only 60% of patients recover in one year and 70-80% in two years (7, 9, 14-19).

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

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

25.

26.

27. **Vascular heart disease and late-life depression**

28.

29. Once, mind, spirit and emotion were thought to center in the heart. That it is the heart
30. which suffers pain and feels anxiety. (Bible Isaiah 65:14, Jeremiah 24:7, Luke 2:19; Rom
31. 5:5; Anonymous writer (Hippocrates?) On the Sacred Disease, c. 425 BCE) In modern
32. times, the relationship between heart and emotional well-being is still topic of many
33. studies (20). Cross-sectional studies show that depression is more common in patients
34. with cardiovascular disease than in the general population (20-23). This was found for
35. heart failure, myocardial infarction and atrial fibrillation. However, little is known about
36. the longitudinal relationship between these diseases and depression. There may be an
37. increased risk of depression in individuals with cardiac disease, an increased risk of cardiac
38. disease in individuals with depression, or both. Only few prospective studies have been
39. performed to test these hypotheses.

1. Depression has also been associated with medications that are prescribed for these cardiac
2. diseases, such as beta-blockers (24, 25). What is known about the use of cardiovascular
3. medication and the risk of depression has been studied in clinical populations primarily.
4. Moreover, elderly patients are rarely included in randomized trials. Yet, approximately
5. 60% of elderly persons take one or more of these drugs regularly. A drug-induced de-
6. pressive disorder would be a preventable or treatable disease in those patients who are
7. vulnerable to this adverse effect, especially because alternative drugs are usually available.

8.

9.

10. **Vascular brain disease and late-life depression**

11.

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

21.

22.

23. **Aim and outline**

24.

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

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

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

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8. References

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1. APA. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR). Washington DC: APA, 2000.
2. Wells KB, Stewart A, Hays RD, et al. The functioning and well-being of depressed patients. Results from the Medical Outcomes Study. *Jama* 1989;262:914-919.
3. Beekman AT, Copeland JR, Prince MJ. Review of community prevalence of depression in later life. *Br J Psychiatry* 1999;174:307-311.
4. Jorm AF. Does old age reduce the risk of anxiety and depression? A review of epidemiological studies across the adult life span. *Psychol Med* 2000;30:11-22.
5. Mulsant BH, Ganguli M. Epidemiology and diagnosis of depression in late life. *J Clin Psychiatry* 1999;60 Suppl 20:9-15.
6. Beekman AT, Geerlings SW, Deeg DJ, et al. The natural history of late-life depression: a 6-year prospective study in the community. *Arch Gen Psychiatry* 2002;59:605-611.
7. Kohn R, Epstein-Lubow G. Course and outcomes of depression in the elderly. *Curr Psychiatry Rep* 2006;8:34-40.
8. Kruijshaar ME, Barendregt J, Vos T, de Graaf R, Spijker J, Andrews G. Lifetime prevalence estimates of major depression: an indirect estimation method and a quantification of recall bias. *Eur J Epidemiol* 2005;20:103-111.
9. Palsson S, Skoog I. The epidemiology of affective disorders in the elderly: a review. *Int Clin Psychopharmacol* 1997;12 Suppl 7:S3-13.
10. Rowe SK, Rapaport MH. Classification and treatment of sub-threshold depression. *Curr Opin Psychiatry* 2006;19:9-13.
11. Copeland JR, Beekman AT, Braam AW, et al. Depression among older people in Europe: the EURODEP studies. *World Psychiatry* 2004;3:45-49.
12. Lepine JP, Bouchez S. Epidemiology of depression in the elderly. *Int Clin Psychopharmacol* 1998;13 Suppl 5:S7-12.
13. Sartorius N. The economic and social burden of depression. *J Clin Psychiatry* 2001;62 Suppl 15:8-11.
14. Alexopoulos GS, Young RC, Abrams RC, Meyers B, Shamoian CA. Chronicity and relapse in geriatric depression. *Biol Psychiatry* 1989;26:551-564.
15. Cole MG, Bellavance F. The prognosis of depression in old age. *Am J Geriatr Psychiatry* 1997;5:4-14.
16. Cole MG, Bellavance F, Mansour A. Prognosis of depression in elderly community and primary care populations: a systematic review and meta-analysis. *Am J Psychiatry* 1999;156:1182-1189.
17. Schoevers RA, Beekman AT, Deeg DJ, Hooijer C, Jonker C, van Tilburg W. The natural history of late-life depression: results from the Amsterdam Study of the Elderly (AMSTEL). *J Affect Disord* 2003;76:5-14.
18. Smits F, Smits N, Schoevers R, Deeg D, Beekman A, Cuijpers P. An epidemiological approach to depression prevention in old age. *Am J Geriatr Psychiatry* 2008;16:444-453.

1. 19. van Weel-Baumgarten EM, Schers HJ, van den Bosch WJ, van den Hoogen HJ, Zitman FG. Long-term follow-up of depression among patients in the community and in family practice settings. A systematic review. *J Fam Pract* 2000;49:1113-1120.
- 2.
3. 20. Carney RM, Freedland KE. Depression, mortality, and medical morbidity in patients with coronary heart disease. *Biol Psychiatry* 2003;54:241-247.
- 4.
5. 21. Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. *J Am Coll Cardiol* 2006;48:1527-1537.
- 6.
7. 22. Thrall G, Lip GY, Carroll D, Lane D. Depression, anxiety, and quality of life in patients with atrial fibrillation. *Chest* 2007;132:1259-1264.
- 8.
9. 23. Thomas SA, Friedmann E, Khatta M, Cook LK, Lann AL. Depression in patients with heart failure: physiologic effects, incidence, and relation to mortality. *AACN Clin Issues* 2003;14:3-12.
10. 24. Steffensmeier JJ, Ernst ME, Kelly M, Hartz AJ. Do randomized controlled trials always trump case reports? A second look at propranolol and depression. *Pharmacotherapy* 2006;26:162-167.
11. 25. Thiessen BQ, Wallace SM, Blackburn JL, Wilson TW, Bergman U. Increased prescribing of antidepressants subsequent to beta-blocker therapy. *Arch Intern Med* 1990;150:2286-2290.
12. 26. Durand-Fardel M. *Traite du Ramollissement da Cerveau*. Paris: Balliere, 1843.
13. 27. Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M. 'Vascular depression' hypothesis. *Arch Gen Psychiatry* 1997;54:915-922.
14. 28. Krishnan KR, Hays JC, Blazer DG. MRI-defined vascular depression. *Am J Psychiatry* 1997;154:497-501.
15. 29. Krishnan KR, McDonald WM. Arteriosclerotic depression. *Med Hypotheses* 1995;44:111-115.
16. 30. Baldwin RC. Is vascular depression a distinct sub-type of depressive disorder? A review of causal evidence. *Int J Geriatr Psychiatry* 2005;20:1-11.
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Chapter 2

Incidence and recurrence of late-life depression



1. **Abstract**

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

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

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

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

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

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

20. *Results.* During the follow-up period of 8 years on average, 566 depressive syndromes and
21. 1073 episodes of clinically relevant depressive symptoms occurred. For depressive syn-
22. dromes, the incidence rate was 7 (95% CI: 6-8) per 1,000 person-years and the recurrence
23. rate was 28 (95% CI: 24-32) per 1,000 person-years. The incidence and recurrence rate
24. more than doubled when episodes of depressive symptoms were included. The recurrence
25. rate of depressive syndromes was equal for women and men, but all other rates were
26. almost twice as high for women compared to men. None of the rates changed with age.

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

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1. Introduction

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

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

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

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

38.

39.

1. **Methods**

2.

3. **Setting**

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

10. So far, four examination rounds have taken place from 1990-1993, 1993-1995, 1997-
11. 1999, and 2002-2004. Participants underwent an extensive home interview and a physical
12. examination at the research centre. Continuous monitoring for major events that oc-
13. curred during follow-up was achieved through linkage with the medical files from general
14. practitioners. These files contain all medical information as the Dutch health care system
15. requires all residents to be registered with a general practitioner (GP) and specialists report
16. back to the GP. Information on vital status was obtained bimonthly from the municipal
17. authorities in Rotterdam.

18.

19. **Study population**

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

25. Of these 6476 participants, 4940 were screened for depressive symptoms, 1372 did not
26. receive a questionnaire containing the screening instrument for depressive symptoms and
27. 164 did not complete the screening questionnaire. However, 829 of these 1536 non-screened
28. persons were successfully screened in the next examination round. Of the remaining 707
29. persons, 339 had died before this round and 395 were lost to follow-up or refused further
30. participation. Thus, 5769 persons (4940+829) were screened for depressive symptoms.

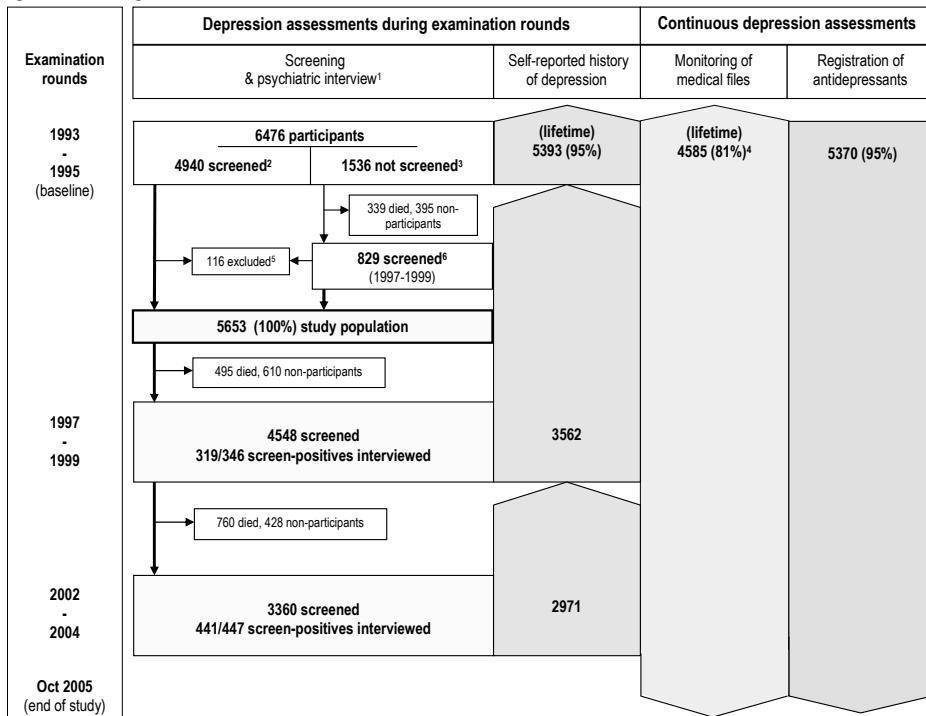
31. We excluded 105 persons with dementia at baseline according to earlier published crite-
32. ria (28), 9 persons that had been diagnosed with bipolar disorder before or after baseline,
33. and 2 persons who died on the day they had been screened. This resulted in a cohort of
34. 5,653 persons for the analysis.

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

38.

39.

Figure 1 Flow diagram



22. **Assessment of depression**

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

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

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

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

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

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

35.

36. **Categorization of depression**

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

1. egorization of depression that reflects this variation in severity and diagnostic approach.
2. Our categorization consisted of two categories: depressive syndromes, including DSM-IV
3. depressive disorders, and clinically relevant depressive symptoms.
4. 1- The category depressive syndromes consisted of 'MDD and dysthymia' and 'other
5. depressive syndromes'. 'MDD and dysthymia' encompassed depressive episodes that
6. clearly met the DSM-IV criteria for these disorders. Furthermore, the episodes were
7. diagnosed by a psychiatrist or another mental health professional - be it in special-
8. ist health care or by psychiatric interview as part of the Rotterdam Study. The group
9. 'other depressive syndromes' covered a) depression recorded by a GP or physician, b)
10. self-reported depression for which the participant consulted a GP or a mental health
11. professional, and c) DSM-IV minor depression.
12. 2- The category clinically relevant depressive symptoms included a) one clinically relevant
13. core symptom of major depression recorded during the psychiatric interview or in the
14. medical record, b) self-reported depression of a participant who did not consult a GP
15. or a mental health professional, and c) initiation of anti-depressant drug treatment
16. (without documentation of clinical symptoms).
17. We applied the same criteria to categorize depressions that preceded the study period.
18. Grief, adjustment disorder and burnout, characterized by emotional exhaustion, and
19. reduced satisfaction in personal accomplishment (33), were not regarded depressions.
20. *Recurrent episodes.* We assumed that a person had recovered fully if no depressive symp-
21. toms had been recorded nor any anti-depressant had been used for a period of at least two
22. years.(34) This two-year criterion not only reflects a conservative approach, but was also
23. deemed appropriate because depression often has a chronic course, with only 60% of
24. patients recovering in one year and 70-80% in two years.(6, 12, 21, 22, 35-38) This way,
25. we took into account that ongoing depressive episodes are frequently poorly documented
26. in primary care medical records, and that a long lag time exists between the onset of a
27. depressive episode and its presentation to a GP. Ideally, actual cessation dates are used, but
28. these are difficult to ascertain in population-based studies.
29. *Date-of-onset.* We defined the date-of-onset of a depressive episode as (a) the self-
30. reported date-of-onset as provided in the psychiatric interview or the self-reported history
31. of depression, (b) the first occurrence of a depressive symptom in the medical records,
32. or (c) the day at which the first prescription of an antidepressant drug was dispensed.
33. *Duplicate reports.* When an episode was identified with two or more assessment methods,
34. we used the most specific assessment method to determine the diagnosis, i.e. the psychi-
35. atric interview overrules the medical records, which in turn overrules the self-reported
36. histories and prescription data. We took the earliest date to define the date-of-onset, with
37. the exception that a date reported retrospectively in the history of depression could not
38. overrule a date from any other assessment method.
- 39.

1. **Data-analysis**

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

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

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

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

32. Finally, we compared the 736 persons who refused to participate at baseline to the 6476
33. responders. Similarly, we compared the 1536 participants who were not screened in the
34. 1993-1995 baseline examination round to the 4940 screened participants.

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1. Results

2.

3. At baseline, the study population consisted of 2,945 (59%) women and 2,159 men. The
 4. mean age was 70 years (range of 56 to 102 years), 63 % of the participants were married
 5. or living together, and 20% had primary school only. The participants lived independently
 6. (97%) or in an assisted living facility (3%). In total, 1,744 persons died during the follow-
 7. up period. The mean follow-up period was 8.0 years.

8. In the follow-up period, 2,093 new-onset depressions were identified. After discarding
 9. 454 duplicate reports, 1,639 episodes remained. Table 1 displays the number of episodes
 10. that were identified with each assessment method. All methods contributed considerably
 11. to the number of episodes identified. Of these episodes 174 were categorized as MDD
 12. or dysthymia, 392 as another depressive syndrome, and the remaining 1,073 as clini-
 13. cally relevant depressive symptoms. Two-thirds of the episodes (1080) involved recurrent
 14. episodes. 216 persons experienced more than one episode during the follow-up period.

15.

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

17. Assessment method	18. Depressive syndromes		19. Depressive symptoms	All depressive episodes (%)
	20. MDD and dysthymia	21. Other depressive syndromes		
22. Psychiatric examination	133	83	178	394 (24)
23. Medical records	41	89	122	252 (15)
24. Self-reported history	NA	220	115	335 (20)
25. Anti-depressant use	NA	NA	658	658 (40)
26. Total	174	392	1073	1639 (100)

27.

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

31.

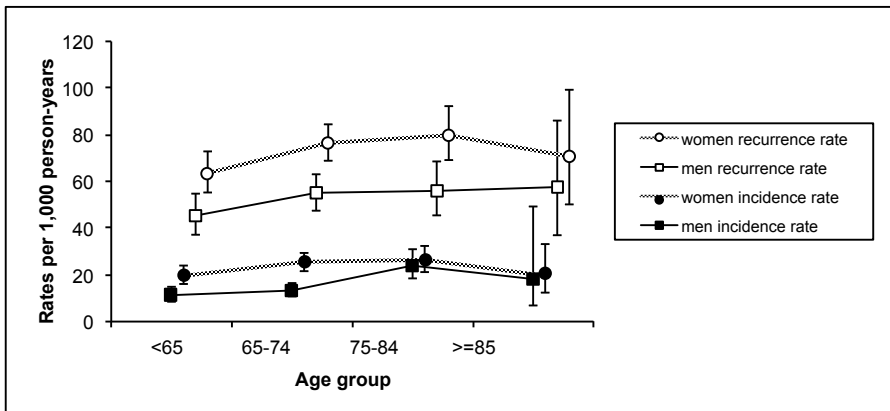
32. Table 2 presents the overall and sex-specific incidence and recurrence rates for episodes
 33. of depressive syndromes and clinically relevant depressive symptoms combined. The
 34. overall incidence rate was 19.3 per 1,000 person-years (95% CI: 17.8-21.0). The Cox'
 35. proportional hazards regression generated an age-adjusted female-to-male ratio of 1.56
 36. (95% CI: 1.31-1.86). The recurrence rate was 65.6 per 1,000 person-years (95% CI:
 37. 61.8-69.7). Thus, the rate of any new-onset depression in participants with a positive
 38. history is more than three times higher than the rate in participants with no history. The
 39. age-adjusted female-to-male ratio was 1.39 (95% CI: 1.21-1.59) for the recurrence rate.
 40. Figure 2 shows that the incidence and recurrence rates appeared to be relatively stable
 41. across 10-year age groups.

42.

43. Table 3 shows the overall and sex-specific incidence and recurrence rates for depressive
 44. 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

1. When re-estimating the recurrence rates using a one- and three-year criterion instead
 2. of a two-year criterion for the definition of a recurrent episode, the overall rate for all
 3. episode combined changed from 65.6 (95% CI: 61.8-69.7) to 76.9 (95% CI: 73.0-81.1)
 4. and 60.8 (95% CI: 57.0-64.8) per 1,000 person-years, respectively. Likewise, the overall
 5. rate of 27.5 (95% CI: 23.7-32.1) for depressive syndromes only, became 30.1 (95% CI:
 6. 26.2-34.6) using a one-year and 21.0 (95% CI: 17.4-25.4) per 1,000 person-years using
 7. a two-year criterion.

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

15. Discussion

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

24. Before discussing our findings, we point out the strengths and weaknesses of our study.
 25. First, this is a large study population with a long follow-up time, which enhances the
 26. accuracy of the estimates. Second, in order to overcome recall problems, we combined
 27. several assessment methods to enhance the detection of incident cases. During the follow-
 28. up rounds an extensive psychiatric assessment was applied, and a self-reported history of
 29. depression was recorded. As older patients are less likely to acknowledge having affective
 30. symptoms (39), we chose the CES-D as screening instrument; it has been validated in
 31. elderly populations, and yields small numbers of false-negatives when using a cut-off of
 32. 16.(30, 40) The SCAN interview method has a high sensitivity compared to the DIS and
 33. CIDI, especially in elderly populations, and provides accurate DSM-IV defined diagnoses.
 34. (41-43)

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

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

12. Automatic registration of filled prescriptions not only has the advantages of prospective
13. methods, the data are also particularly useful to specify the date-of-onset of episodes.
14. In some etiological studies, antidepressant use is used as an indicator of a depressive
15. syndrome.(52, 53) However, modern antidepressants are commonly prescribed for other
16. indications such as anxiety disorders, sleeping disorders, migraine, or neuropathic pain.
17. (54, 55) Population surveys and family practices studies have shown that 43-56% of
18. patients receiving an antidepressant do not fulfill the criteria of depression.(54, 56-58)
19. Hence, we regarded antidepressant use as a marker of depressive symptoms only.

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

33. Our study yielded lower incidence rates than those presented by other studies in elderly
34. populations. In our study the incidence rate for major depression and dysthymia was 2 per
35. 1,000 person-years (95% CI: 2-3), while the Cache County study presented an incidence
36. rate for major depression of 8 per 1,000 person-years (95% CI: 6-11). To some extent,
37. this higher incidence rate is explained by the diagnoses of depression that were made in
38. interviews with family and caregivers of deceased participants (20% of total). Similarly,
39. in our study the incidence rate for depressive syndromes, including major depression,

1. dysthymia and minor depression, was 7 per 1,000 person-years (95% CI: 6-8), whereas
2. the Göteborg study yielded an incidence rate for major depression, dysthymia and depres-
3. sion NOS of 23 per 1,000 person-years (95% CI: 18-29). This study differed from ours
4. in that it was performed more than 20 years ago in a relatively small birth cohort of 322
5. persons born in 1901-1902. Most likely though, our lower estimates resulted from our
6. conservative approach in categorizing depressive episodes as being a depressive syndrome.
7. In addition, our study population may have included fewer participants with misclassi-
8. fied negative histories, because data was available on the occurrence of depression in the
9. period between the start of the study and the first follow-up examination, which served
10. as baseline for our analysis of depressive syndromes. Indeed, the incidence rate of depres-
11. sive syndromes and symptoms combined that we found seems more in line with that of
12. the abovementioned Cache County study: 19 per 1,000 person-years (95% CI: 18-21)
13. compared to 24 per 1,000 person-years (95% CI: 20-27) respectively.(20) In particular as
14. 20% of the depression cases in the latter study involved bereavement. Finally, some studies
15. have found that late-life depression is more often characterized by somatic and cognitive
16. symptoms, even though others found no differences.(59-62) As the conventional core
17. symptoms of depression in the DSM are important for our categorization, the incidence
18. and recurrence rates that we present are probably conservative estimates.

19. Some landmark studies performed among mixed-age populations in North-America
20. and Scandinavia, such as the Epidemiologic Catchment Area Study, the Lundby Study,
21. and the Stirling County Study have also estimated incidence rates of major depression
22. in the elderly subgroups. The most recently published analyses show incidence rates for
23. major depression between 0.9 and 4.5 per 1,000 person-years.(8-10) We found an inci-
24. dence rate for major depression and dysthymia of 2 per 1,000 person-years (95% CI: 2-3).
25. The results seem similar to ours, even though in the cited studies psychiatric assessments
26. were generally based on the DIS, intervals between follow-up rounds were much longer
27. (11 to 40 years), continuous monitoring during the intervals was generally lacking, and
28. demented participants were not excluded.

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

1. depressive episodes diagnosed are first ever episodes. This emphasizes the importance of
2. maintenance treatment and close monitoring after recovery from depression.
3. We found that men had similar risks for a recurrent depressive syndrome as women,
4. even though the female-to-male ratios of the other rates that we studied were in line with
5. the well-known ratio of 1.5-3.0.(67, 68) In adult populations no significant sex differences
6. in the course of major depressive disorder were found as well.(65, 69) Prospective studies
7. among adult populations have shown rather consistently that psychological and social risk
8. factors such as higher levels of anxiety, lower self-confidence, lack of power, role strain and
9. sexual abuse contribute to the higher risk of first-ever depression in women.(70, 71) In
10. addition, men seem to recollect less episodes of depression and underreport the severity
11. of symptoms compared to women.(72, 73) Studies that investigated gender differences
12. in late-life depression are scarce. One study suggested that depressed older men were less
13. likely to endorse core depressive symptoms or to be referred for treatment.(74) Appar-
14. ently, risk factors for incident depressions do not always predict the course of depression
15. as well. The risk factors for recurrent late-life depression are possibly less gender related,
16. and recurrent depressive syndromes might be as easily recognized in men as in women.
17. In conclusion, if a person has never had a depression in middle age, his risk of devel-
18. oping a first-ever episode in old age may be lower than estimated before. Conversely,
19. if someone has experienced a depression before, the risk of a recurrent episode in old
20. age is high. In fact, the majority of new episodes in our study were recurrent episodes.
21. These findings, in addition to the chronic nature of depression, could explain the well-
22. known discrepancy between the high prevalence and low incidence of late-life depression.
23. Community-dwelling elderly persons have a much higher risk of developing a recurrent
24. than a first ever depression. To enhance diagnostic accuracy, it is thus important that
25. clinicians become aware of this a priori risk. More research is needed to clarify the etiology
26. of recurring late-life depression, given that recurring episodes contribute substantially to
27. the impact of depression on public health.

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30. **References**

31. 1. Beekman AT, Copeland JR, Prince MJ. Review of community prevalence of depression in later life. *Br J*
32. *Psychiatry* 1999;174:307-11.
33. 2. Copeland JR, Beekman AT, Braam AW, Dewey ME, Delespaul P, Fuhrer R, Hooijer C, Lawlor BA,
34. Kivela SL, Lobo A, Magnusson H, Mann AH, Meller I, Prince MJ, Reischies F, Roelands M, Skoog
35. I, Turrina C, deVries MW, Wilson KC. Depression among older people in Europe: the EURODEP
36. studies. *World Psychiatry* 2004;3:45-9.
37. 3. Mulsant BH, Ganguli M. Epidemiology and diagnosis of depression in late life. *J Clin Psychiatry*
38. 1999;60 Suppl 20:9-15.
39. 4. Sartorius N. The economic and social burden of depression. *J Clin Psychiatry* 2001;62 Suppl 15:8-11.

1. 5. Lepine JP, Bouchez S. Epidemiology of depression in the elderly. *Int Clin Psychopharmacol* 1998;13 Suppl 5:S7-12.
2. 6. Palsson S, Skoog I. The epidemiology of affective disorders in the elderly: a review. *Int Clin Psychopharmacol* 1997;12 Suppl 7:S3-13.
3. 7. Burvill PW. Recent progress in the epidemiology of major depression. *Epidemiol Rev* 1995;17:21-31.
4. 8. Mattisson C, Bogren M, Nettelblatt P, Munk-Jorgensen P, Bhugra D. First incidence depression in the Lundby Study: a comparison of the two time periods 1947-1972 and 1972-1997. *J Affect Disord* 2005;87:151-60.
5. 9. Murphy JM, Laird NM, Monson RR, Sobol AM, Leighton AH. Incidence of depression in the Stirling County Study: historical and comparative perspectives. *Psychol Med* 2000;30:505-14.
6. 10. Eaton WW, Kalaydjian A, Scharfstein DO, Mezuk B, Ding Y. Prevalence and incidence of depressive disorder: the Baltimore ECA follow-up, 1981-2004. *Acta Psychiatr Scand* 2007;116:182-8.
7. 11. Jorm AE. Does old age reduce the risk of anxiety and depression? A review of epidemiological studies across the adult life span. *Psychol Med* 2000;30:11-22.
8. 12. Kohn R, Epstein-Lubow G. Course and outcomes of depression in the elderly. *Curr Psychiatry Rep* 2006;8:34-40.
9. 13. Magruder KM, Calderone GE. Public health consequences of different thresholds for the diagnosis of mental disorders. *Compr Psychiatry* 2000;41:14-8.
10. 14. Rowe SK, Rapaport MH. Classification and treatment of sub-threshold depression. *Curr Opin Psychiatry* 2006;19:9-13.
11. 15. Tannock C, Katona C. Minor depression in the aged. Concepts, prevalence and optimal management. *Drugs Aging* 1995;6:278-92.
12. 16. Snowdon J, Lane, F. The prevalence and outcome of depression and dementia in Botany's elderly population. *Int J Geriatr Psychiatry* 1995;16:293-9.
13. 17. Simon GE, VonKorff M. Recall of psychiatric history in cross-sectional surveys: implications for epidemiologic research. *Epidemiol Rev* 1995;17:221-7.
14. 18. Kruijshaar ME, Barendregt J, Vos T, de Graaf R, Spijker J, Andrews G. Lifetime prevalence estimates of major depression: an indirect estimation method and a quantification of recall bias. *Eur J Epidemiol* 2005;20:103-11.
15. 19. Palsson SP, Ostling S, Skoog I. The incidence of first-onset depression in a population followed from the age of 70 to 85. *Psychol Med* 2001;31:1159-68.
16. 20. Norton MC, Skoog I, Toone L, Corcoran C, Tschanz JT, Lisota RD, Hart AD, Zandi PP, Breitner JC, Welsh-Bohmer KA, Steffens DC. Three-year incidence of first-onset depressive syndrome in a population sample of older adults: the Cache County study. *Am J Geriatr Psychiatry* 2006;14:237-45.
17. 21. Alexopoulos GS, Young RC, Abrams RC, Meyers B, Shamoian CA. Chronicity and relapse in geriatric depression. *Biol Psychiatry* 1989;26:551-64.
18. 22. Cole MG, Bellavance F. The prognosis of depression in old age. *Am J Geriatr Psychiatry* 1997;5:4-14.
19. 23. Mueller TI, Kohn R, Leventhal N, Leon AC, Solomon D, Coryell W, Endicott J, Alexopoulos GS, Keller MB. The course of depression in elderly patients. *Am J Geriatr Psychiatry* 2004;12:22-9.
20. 24. Reynolds CF, 3rd, Dew MA, Frank E, Begley AE, Miller MD, Cornes C, Mazumdar S, Perel JM, Kupfer DJ. Effects of age at onset of first lifetime episode of recurrent major depression on treatment response and illness course in elderly patients. *Am J Psychiatry* 1998;155:795-9.
21. 25. Reynolds CF, 3rd, Frank E, Perel JM, Imber SD, Cornes C, Miller MD, Mazumdar S, Houck PR, Dew MA, Stack JA, Pollock BG, Kupfer DJ. Nortriptyline and interpersonal psychotherapy as maintenance therapies for recurrent major depression: a randomized controlled trial in patients older than 59 years. *Jama* 1999;281:39-45.

1. 26. Reynolds CF, 3rd, Dew MA, Pollock BG, Mulsant BH, Frank E, Miller MD, Houck PR, Mazumdar S, Butters MA, Stack JA, Schlernitzauer MA, Whyte EM, Gildengers A, Karp J, Lenze E, Szanto K, Bensasi S, Kupfer DJ. Maintenance treatment of major depression in old age. *N Engl J Med* 2006;354:1130-8.
2. 27. Hofman A, Breteler MM, van Duijn CM, Krestin GP, Pols HA, Stricker BH, Tiemeier H, Uitterlinden AG, Vingerling JR, Witteman JC. The Rotterdam Study: objectives and design update. *Eur J Epidemiol* 2007;22:819-29.
3. 28. Ott A, Breteler MM, van Harskamp F, Stijnen T, Hofman A. Incidence and risk of dementia. The Rotterdam Study. *Am J Epidemiol* 1998;147:574-80.
4. 29. Herrmann C. International experiences with the Hospital Anxiety and Depression Scale--a review of validation data and clinical results. *J Psychosom Res* 1997;42:17-41.
5. 30. Beekman AT, Deeg DJ, Van Limbeek J, Braam AW, De Vries MZ, Van Tilburg W. Criterion validity of the Center for Epidemiologic Studies Depression scale (CES-D): results from a community-based sample of older subjects in The Netherlands. *Psychol Med* 1997;27:231-5.
6. 31. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res* 2002;52:69-77.
7. 32. WHO. SCAN Schedules for Clinical Assessment in Neuropsychiatry, Version 2.1. 2nd ed. Geneva: World Health Organisation; 1997.
8. 33. Weber A, Jaekel-Reinhard A. Burnout syndrome: a disease of modern societies? *Occup Med (Lond)* 2000;50:512-7.
9. 34. Rush AJ, Kraemer HC, Sackeim HA, Fava M, Trivedi MH, Frank E, Ninan PT, Thase ME, Gelenberg AJ, Kupfer DJ, Regier DA, Rosenbaum JF, Ray O, Schatzberg AF, Force AT. Report by the ACNP Task Force on response and remission in major depressive disorder. *Neuropsychopharmacology* 2006;31:1841-53.
10. 35. Cole MG, Bellavance F, Mansour A. Prognosis of depression in elderly community and primary care populations: a systematic review and meta-analysis. *Am J Psychiatry* 1999;156:1182-9.
11. 36. Schoevers RA, Beekman AT, Deeg DJ, Hooijer C, Jonker C, van Tilburg W. The natural history of late-life depression: results from the Amsterdam Study of the Elderly (AMSTEL). *J Affect Disord* 2003;76:5-14.
12. 37. Smits F, Smits N, Schoevers R, Deeg D, Beekman A, Cuijpers P. An epidemiological approach to depression prevention in old age. *Am J Geriatr Psychiatry* 2008;16:444-53.
13. 38. van Weel-Baumgarten EM, Schers HJ, van den Bosch WJ, van den Hoogen HJ, Zitman FG. Long-term follow-up of depression among patients in the community and in family practice settings. A systematic review. *J Fam Pract* 2000;49:1113-20.
14. 39. Lyness JM, Cox C, Curry J, Conwell Y, King DA, Caine ED. Older age and the underreporting of depressive symptoms. *J Am Geriatr Soc* 1995;43:216-21.
15. 40. Watson LC, Lewis CL, Kistler CE, Amick HR, Boustani M. Can we trust depression screening instruments in healthy 'old-old' adults? *Int J Geriatr Psychiatry* 2004;19:278-85.
16. 41. Aalto-Setälä T, Haarasilta L, Marttunen M, Tuulio-Henriksson A, Poikolainen K, Aro H, Lonnqvist J. Major depressive episode among young adults: CIDI-SF versus SCAN consensus diagnoses. *Psychol Med* 2002;32:1309-14.
17. 42. Eaton WW, Neufeld K, Chen LS, Cai G. A comparison of self-report and clinical diagnostic interviews for depression: diagnostic interview schedule and schedules for clinical assessment in neuropsychiatry in the Baltimore epidemiologic catchment area follow-up. *Arch Gen Psychiatry* 2000;57:217-22.
18. 43. Bebbington P. The Classification and Epidemiology of Unipolar Depression. In Power M editor. *Mood Disorders: A Handbook of Science and Practice*. Hoboken, NJ: John Wiley & Sons, Ltd.; 2003.
19. 39.

1. 44. Giuffra LA, Risch N. Diminished recall and the cohort effect of major depression: a simulation study. *Psychol Med* 1994;24:375-83.
2. 45. Docherty JP. Barriers to the diagnosis of depression in primary care. *J Clin Psychiatry* 1997;58 Suppl 1:5-10.
3. 46. Fischer LR, Wei F, Solberg LI, Rush WA, Heinrich RL. Treatment of elderly and other adult patients for depression in primary care. *J Am Geriatr Soc* 2003;51:1554-62.
4. 47. Wittchen HU, Knauper B, Kessler RC. Lifetime risk of depression. *Br J Psychiatry Suppl* 1994:16-22.
5. 48. Lecrubier Y. Widespread underrecognition and undertreatment of anxiety and mood disorders: results from 3 European studies. *J Clin Psychiatry* 2007;68 Suppl 2:36-41.
6. 49. Simon GE, VonKorff M. Recognition, management, and outcomes of depression in primary care. *Arch Fam Med* 1995;4:99-105.
7. 50. Tylee A, Walters P. Underrecognition of anxiety and mood disorders in primary care: why does the problem exist and what can be done? *J Clin Psychiatry* 2007;68 Suppl 2:27-30.
8. 51. Terluin B, van Hout HP, van Marwijk HW, Ader HJ, van der Meer K, de Haan M, van Dyck R. Reliability and validity of the assessment of depression in general practice: the Short Depression Interview (SDI). *Gen Hosp Psychiatry* 2002;24:396-405.
9. 52. Thiessen BQ, Wallace SM, Blackburn JL, Wilson TW, Bergman U. Increased prescribing of antidepressants subsequent to beta-blocker therapy. *Arch Intern Med* 1990;150:2286-90.
10. 53. Avorn J, Everitt DE, Weiss S. Increased antidepressant use in patients prescribed beta-blockers. *Jama* 1986;255:357-60.
11. 54. Ohayon MM, Lader MH. Use of psychotropic medication in the general population of France, Germany, Italy, and the United Kingdom. *J Clin Psychiatry* 2002;63:817-25.
12. 55. Patten SB, Esposito E, Carter B. Reasons for antidepressant prescriptions in Canada. *Pharmacoepidemiol Drug Saf* 2007;16:746-52.
13. 56. Gardarsdottir H, Heerdink ER, van Dijk L, Egberts AC. Indications for antidepressant drug prescribing in general practice in the Netherlands. *J Affect Disord* 2007;98:109-15.
14. 57. Beck CA, Patten SB, Williams JV, Wang JL, Currie SR, Maxwell CJ, El-Guebaly N. Antidepressant utilization in Canada. *Soc Psychiatry Psychiatr Epidemiol* 2005;40:799-807.
15. 58. Ornstein S, Stuart G, Jenkins R. Depression diagnoses and antidepressant use in primary care practices: a study from the Practice Partner Research Network (PPRNet). *J Fam Pract* 2000;49:68-72.
16. 59. Christensen H, Jorm AF, Mackinnon AJ, Korten AE, Jacomb PA, Henderson AS, Rodgers B. Age differences in depression and anxiety symptoms: a structural equation modelling analysis of data from a general population sample. *Psychol Med* 1999;29:325-39.
17. 60. Gallo JJ, Anthony JC, Muthen BO. Age differences in the symptoms of depression: a latent trait analysis. *J Gerontol* 1994;49:P251-64.
18. 61. Katona C, Livingston G, Manela M, Leek C, Mullan E, Orrell M, D'Ath P, Zeitlin D. The symptomatology of depression in the elderly. *Int Clin Psychopharmacol* 1997;12 Suppl 7:S19-23.
19. 62. Reischies FM, von Spiess P, Stieglitz RD. The symptom pattern variations of unipolar depression during life span: a cross-sectional study. *Compr Psychiatry* 1990;31:457-64.
20. 63. Mitchell AJ, Subramaniam H. Prognosis of depression in old age compared to middle age: a systematic review of comparative studies. *Am J Psychiatry* 2005;162:1588-601.
21. 64. Solomon DA, Keller MB, Leon AC, Mueller TI, Lavori PW, Shea MT, Coryell W, Warshaw M, Turvey C, Maser JD, Endicott J. Multiple recurrences of major depressive disorder. *Am J Psychiatry* 2000;157:229-33.
22. 65. Eaton WW, Shao H, Nestadt G, Lee BH, Bienvenu OJ, Zandi P. Population-based study of first onset and chronicity in major depressive disorder. *Arch Gen Psychiatry* 2008;65:513-20.

66. Lee AS. Better outcomes for depressive disorders? *Psychol Med* 2003;33:769-74.
1. 67. Cole MG, Dendukuri N. Risk factors for depression among elderly community subjects: a systematic review and meta-analysis. *Am J Psychiatry* 2003;160:1147-56.
2. 68. Bland RC. Epidemiology of affective disorders: a review. *Can J Psychiatry* 1997;42:367-77.
3. 69. Mattisson C, Bogren M, Horstmann V, Munk-Jorgensen P, Nettelbladt P. The long-term course of depressive disorders in the Lundby Study. *Psychol Med* 2007;37:883-91.
4. 70. Piccinelli M, Wilkinson G. Gender differences in depression. Critical review. *Br J Psychiatry* 2000;177:486-92.
5. 71. Kuehner C. Gender differences in unipolar depression: an update of epidemiological findings and possible explanations. *Acta Psychiatr Scand* 2003;108:163-74.
6. 72. Ernst C, Angst J. The Zurich Study. XII. Sex differences in depression. Evidence from longitudinal epidemiological data. *Eur Arch Psychiatry Clin Neurosci* 1992;241:222-30.
7. 73. Hunt M, Auriemma J, Cashaw AC. Self-report bias and underreporting of depression on the BDI-II. *J Pers Assess* 2003;80:26-30.
8. 74. Hinton L, Zweifach M, Oishi S, Tang L, Unutzer J. Gender disparities in the treatment of late-life depression: qualitative and quantitative findings from the IMPACT trial. *Am J Geriatr Psychiatry* 2006;14:884-92.
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Part II

**Vascular heart disease and
late-life depression**

Chapter 3

Heart failure



1. **Abstract**

2.

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

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

16. *Results.* Heart failure was associated with an increased risk of depressive symptoms and
17. syndromes combined (HR 1.41; 95% CI 1.03-1.94). It also increased the risk of depres-
18. sive syndromes (HR 1.66; 95% CI 1.09-2.52). In participants with heart failure, the use
19. of loop diuretics more than halved the risk of depressive symptoms and syndromes (HR
20. 0.46; 95% CI 0.22-0.96) and depressive syndromes only (HR 0.41; 95% CI 0.16-1.00).

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

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1. Introduction

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

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

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

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

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1. **Methods**

2.

3. **Setting**

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

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

22.

23. **Study population**

24. During the second visit, the baseline of the current analysis, 5,769 participants were
25. screened for depressive symptoms. Participants filled out either the validated Dutch ver-
26. sion of the Center for Epidemiologic Studies Depression Scale (CES-D) or the validated
27. Dutch version of the Hospital Anxiety and Depression Scale (HADS-D).(16, 17) A score
28. of 16 or higher out of 60 on the CES-D and 9 or higher out of 21 on the HADS-D
29. was considered screen-positive for depressive symptoms.(16, 17) At baseline, we excluded
30. 549 persons with depressive symptoms, 105 persons with dementia (18), 9 persons with
31. bipolar disorder diagnosed before or after baseline, 9 persons with missing heart failure
32. status and 2 persons who were lost-to-follow-up on the day they had been screened. This
33. resulted in a study population of 5,095 persons who were free of depression at baseline.

34.

35. **Assessment of incident depression**

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

1. examination rounds. First, all participants were screened with the CES-D as part of the
2. home-interview. Next, the screen-positive participants were invited for a clinical interview,
3. in which trained clinicians administered a semi-structured psychiatric interview included
4. in the Schedules for Clinical Assessment in Neuropsychiatry (SCAN).(20) Major and mi-
5. nor depressive disorders and dysthymia were ascertained with a computerized algorithm
6. that reflected DSM-IV criteria.(21) The self-reported history of depression was solicited
7. at baseline and during follow-up rounds. Participants were asked standardized questions
8. to assess whether they had suffered from a depressive episode up to that time, and if so
9. whether they had been treated, and at what age the episode had occurred. The GPs' medi-
10. cal records were scrutinized by trained research-assistants. They copied the information
11. that indicated a potential depression. Two research physicians independently assessed this
12. information, and categorized each depressive episode according to a predefined protocol
13. (see below).

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

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

28.

29. **Assessment of heart failure**

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

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

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

16.

17. **Covariates**

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

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

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

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

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

12.

13. **Statistical analysis**

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

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

38.

39.

1. Results

2.
3. Table 1 presents the baseline characteristics of the study sample. The average age was 70
4. years with a range of 56 to 101 years and 58 % of the participants were female. The most
5. prevalent cardiovascular risk factor was history of smoking with 51% former smokers and
6. 17 % current smokers. At baseline, 1641 participants had a history of depression, and 206
7. participants had heart failure. Another 423 persons developed heart failure after baseline
8. during follow-up. In our study population, a total of 736 incident depressions occurred
9. during 42,090 person-years. Of these depressions, 407 were depressive syndromes, includ-
10. ing 103 DSM-defined major depressive disorders and dysthymias. The mean time between
11. onset of heart-failure and onset of depression was 3.5 years (SD 2.9), counting cases of
12. heart failure present at baseline from that time onward.

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

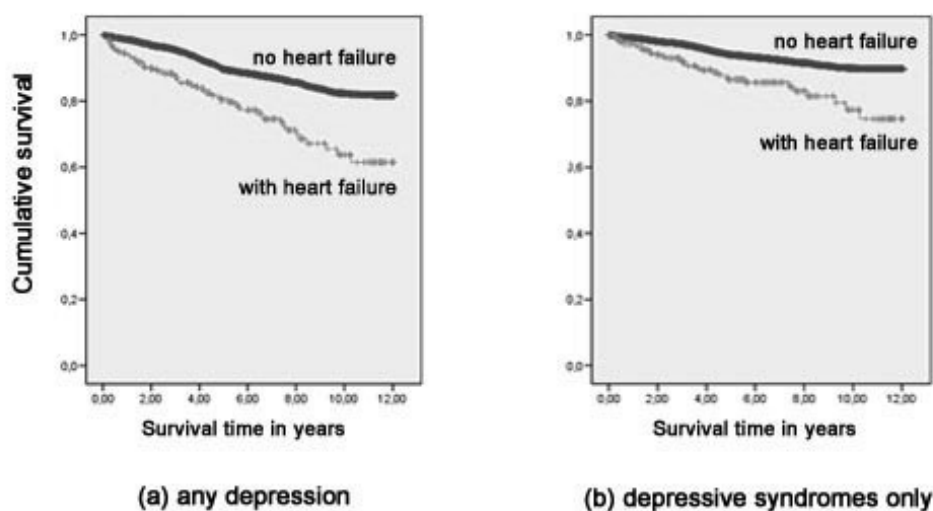
15. Characteristic	Descriptives
16. Socio-demographic factors	
17. Age, mean (SD)	70.0 (8.3)
18. Female, n (%)	2939 (57.7)
19. Education, primary school only, n (%)	934 (18.3)
19. Income, mean (range), in euros/month	1220 (350-3200)
20. Cardiovascular risk factors	
20. Smoking	
21. - former smoker, n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

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

37.
38. Figure 1 depicts the Kaplan-Meier survival curves by heart failure status. After 12 years
39. of follow-up, twice as many participants with heart failure had developed depression than

1. those without heart failure. A similar difference was seen for depressive syndromes only.
 2. Table 2 shows the risk of depression associated with heart failure. Heart failure was associ-
 3. ated with a significantly increased risk of depressive symptoms and syndromes combined
 4. (HR 1.36; 95% CI 1.03-1.81) and depressive syndromes only (HR 1.54; 95% CI 1.06-
 5. 2.24) when age and sex were the sole factors adjusted for. The risk estimates were similar,
 6. that is 1.41 (95% CI 1.03-1.94) for depressive symptoms and syndromes and 1.66 (95%
 7. CI 1.09-2.52) for depressive syndromes, in the models that adjusted for all confounders
 8. and the associations remained significant.

9.
 10. **Figure 1 Kaplan-Meier curves of depression-free survival by heart failure status**



27. **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

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 35. * adjusted for age, sex, SES, ADL, history of depression, smoking, hypertension, diabetes, myocardial infarct, history of other ischemic cardiovascular

36. disease, atrial fibrillation, and use of loop diuretics and other antihypertensive medication.

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

38. ‡ includes DSM-defined depressive disorders

1. Next, we estimated the risk of first-ever incident depression in the persons without
 2. a history of depression at baseline (n=3,454). In the multivariate model, heart failure
 3. again carried an increased risk of depressive symptoms and syndromes (HR 1.64; 95% CI
 4. 1.04-2.58), and depressive syndromes (HR 2.07; 95% CI 1.15-3.72). Moreover, persons
 5. with heart failure had a three-fold, almost significant, risk of first-ever depressive disorders
 6. (HR 3.00; 95% CI 0.86-10.50; not in table) compared to the others.

7. Table 3 presents the risk of depression related to the use of loop diuretics in persons with
 8. heart failure. In the models adjusted for age and sex only, current use of loop diuretics was
 9. not significantly associated with depressive symptoms and syndromes (HR 0.59; 95% CI
 10. 0.30-1.15), nor with depressive syndromes only (HR 0.48; 95% CI 0.22-1.06). However,
 11. the multivariate models indicated similar but just significant associations for both out-
 12. comes, with a more than 50% reduced risk of depressive symptoms and syndromes (HR
 13. 0.46; 95% CI 0.22-0.96) and depressive syndromes only (HR 0.41; 95% CI 0.16-1.00)
 14. in current users of loop diuretics.

15.
 16. **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

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 20.
 21. * adjusted for age, sex, SES, ADL, history of depression, smoking, hypertension, myocardial infarct, history of other ischemic
 22. cardiovascular disease, atrial fibrillation, and use of other antihypertensives.

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

25. ‡ includes DSM-defined depressive disorders

26. Discussion

27.
 28.
 29. The present study demonstrates that people with heart failure had an increased risk of devel-
 30. oping incident depression. The risk remained similarly high when persons with a history of
 31. depression were excluded. Our findings also suggest that the use of loop diuretics in persons
 32. with heart failure decreased the risk of incident depression. Many cross-sectional studies
 33. have shown that depression is very common in heart failure. Our study demonstrated that
 34. heart failure is also a risk factor for incident depression. To the best of our knowledge, there
 35. is only one other prospective study. It showed that 21% of 245 outpatients with heart
 36. failure had depressive symptoms one year later.(31) Patients living alone, reporting alcohol
 37. abuse, perceiving medical care as an economic burden, and those with impaired health
 38. status were more likely to develop depressive symptoms. However, the lack of a control
 39. group forestalled a conclusion about the risk of incident depression in that study.

1. Heart failure is a fatal disease, with only 35%-50% of patients surviving more than
2. 5 years.(22, 32) Experiencing the symptoms of such a life-threatening disease may pro-
3. voke a psychological reaction, and when coping mechanisms fail, a patient may become
4. depressed. Reversely, individuals with high levels of perceived self-control are better able
5. to manage their cardiac disease, which in turn leads to improvement of functional status
6. and thereby to a decrease in depression.(6) In addition, biological mechanisms might
7. explain the increased risk of depression related to heart failure. For instance, reduced
8. cardiac output as a result of heart failure could lead to insufficient cerebral perfusion
9. and the drugs prescribed for it may cause hypotension, dizziness and fatigue that may in
10. turn lead to psychological discomfort.(14) In the current study, use of loop diuretics was
11. associated with a protective effect against depression. As loop diuretics effectively diminish
12. the debilitating symptoms of heart failure, this finding suggests that the symptoms of the
13. disease themselves may account for the increased risk of depression. Finally, evidence exists
14. of a common genetic vulnerability for risk factors of heart failure, such as atherosclerosis
15. and myocardial infarction, and depression.(33)

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

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

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

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

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

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16. References

17. 1. Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure a meta-analytic
 18. review of prevalence, intervention effects, and associations with clinical outcomes. *J Am Coll Cardiol*
 19. 2006;48:1527-1537.

20. 2. MacMahon KM, Lip GY. Psychological factors in heart failure: a review of the literature. *Arch Intern*
 21. *Med* 2002;162:509-516.

22. 3. Vaccarino V, Kasl SV, Abramson J, Krumholz HM. Depressive symptoms and risk of functional decline
 23. and death in patients with heart failure. *J Am Coll Cardiol* 2001;38:199-205.

24. 4. Whooley MA. Depression and cardiovascular disease: healing the broken-hearted. *Jama* 2006;295:2874-
 25. 2881.

26. 5. Egede LE. Major depression in individuals with chronic medical disorders: prevalence, correlates and
 27. association with health resource utilization, lost productivity and functional disability. *Gen Hosp Psy-*
 28. *chiatry* 2007;29:409-416.

29. 6. Konstam V, Moser DK, De Jong MJ. Depression and anxiety in heart failure. *J Card Fail* 2005;11:455-
 30. 463.

31. 7. Thomas SA, Friedmann E, Khatta M, Cook LK, Lann AL. Depression in patients with heart failure:
 32. physiologic effects, incidence, and relation to mortality. *AACN Clin Issues* 2003;14:3-12.

33. 8. Williams SA, Kasl SV, Heiat A, Abramson JL, Krumholz HM, Vaccarino V. Depression and risk of heart
 34. failure among the elderly: a prospective community-based study. *Psychosom Med* 2002;64:6-12.

35. 9. Abramson J, Berger A, Krumholz HM, Vaccarino V. Depression and risk of heart failure among older
 36. persons with isolated systolic hypertension. *Arch Intern Med* 2001;161:1725-1730.

37. 10. de Jonge P, van den Brink RH, Spijkerman TA, Ormel J. Only incident depressive episodes after myo-
 38. cardial infarction are associated with new cardiovascular events. *J Am Coll Cardiol* 2006;48:2204-2208.

39. 11. Holley C, Murrell SA, Mast BT. Psychosocial and vascular risk factors for depression in the elderly. *Am*
 40. *J Geriatr Psychiatry* 2006;14:84-90.

41. 12. Kim JM, Stewart R, Kim SW, Yang SJ, Shin IS, Yoon JS. Vascular risk factors and incident late-life
 42. depression in a Korean population. *Br J Psychiatry* 2006;189:26-30.

1. 13. Paterniti S, Verdier-Taillefer MH, Geneste C, Bisserbe JC, Alperovitch A. Low blood pressure and risk of depression in the elderly. A prospective community-based study. *Br J Psychiatry* 2000;176:464-467.
2. 14. Simpson LO. Symptoms of low blood pressure. *BMJ* 1990;301:815-816.
3. 15. Hofman A, Breteler MM, van Duijn CM, et al. The Rotterdam Study: objectives and design update. *Eur J Epidemiol* 2007;22:819-829.
4. 16. Beekman AT, Deeg DJ, Van Limbeek J, Braam AW, De Vries MZ, Van Tilburg W. Criterion validity of the Center for Epidemiologic Studies Depression scale (CES-D): results from a community-based sample of older subjects in The Netherlands. *Psychol Med* 1997;27:231-235.
5. 17. Herrmann C. International experiences with the Hospital Anxiety and Depression Scale--a review of validation data and clinical results. *J Psychosom Res* 1997;42:17-41.
6. 18. Ott A, Breteler MM, van Harskamp F, Stijnen T, Hofman A. Incidence and risk of dementia. The Rotterdam Study. *Am J Epidemiol* 1998;147:574-580.
7. 19. Luijckendijk HJ, van den Berg JF, Dekker MJ, et al. Incidence and recurrence of late-life depression. *Arch Gen Psychiatry* 2008;65:1394-1401.
8. 20. WHO. SCAN Schedules for Clinical Assessment in Neuropsychiatry, Version 2.1., 2nd ed. Geneva: World Health Organisation, 1997.
9. 21. Association AP. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR). Washington DC: APA, 2000.
10. 22. Bleumink GS, Knetsch AM, Sturkenboom MC, et al. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure The Rotterdam Study. *Eur Heart J* 2004;25:1614-1619.
11. 23. Mosterd A, Hoes AW, de Bruyne MC, et al. Prevalence of heart failure and left ventricular dysfunction in the general population; The Rotterdam Study. *Eur Heart J* 1999;20:447-455.
12. 24. Remme WJ, Swedberg K. Guidelines for the diagnosis and treatment of chronic heart failure. *Eur Heart J* 2001;22:1527-1560.
13. 25. Bloom M. Measurement of the socioeconomic status of the aged: new thoughts on an old subject. *Gerontologist* 1972;12:375-378.
14. 26. Pincus T, Summey JA, Soraci SA, Jr., Wallston KA, Hummon NP. Assessment of patient satisfaction in activities of daily living using a modified Stanford Health Assessment Questionnaire. *Arthritis Rheum* 1983;26:1346-1353.
15. 27. WHO. 1999 World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension. Guidelines Subcommittee. *J Hypertens* 1999;17:151-183.
16. 28. Dehghan A, Kardys I, de Maat MP, et al. Genetic variation, C-reactive protein levels, and incidence of diabetes. *Diabetes* 2007;56:872-878.
17. 29. de Bruyne MC, Mosterd A, Hoes AW, et al. Prevalence, determinants, and misclassification of myocardial infarction in the elderly. *Epidemiology* 1997;8:495-500.
18. 30. Heeringa J, van der Kuip DA, Hofman A, et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart J* 2006;27:949-953.
19. 31. Havranek EP, Spertus JA, Masoudi FA, Jones PG, Rumsfeld JS. Predictors of the onset of depressive symptoms in patients with heart failure. *J Am Coll Cardiol* 2004;44:2333-2338.
20. 32. Levy D, Kenchaiah S, Larson MG, et al. Long-term trends in the incidence of and survival with heart failure. *N Engl J Med* 2002;347:1397-1402.
21. 33. Lopez-Leon S, Janssens AC, Gonzalez-Zuloeta Ladd AM, et al. Meta-analyses of genetic studies on major depressive disorder. *Mol Psychiatry* 2008;13:772-785.
22. 34. Norton MC, Skoog I, Toone L, et al. Three-year incidence of first-onset depressive syndrome in a population sample of older adults: the Cache County study. *Am J Geriatr Psychiatry* 2006;14:237-245.

Chapter 4

Atrial fibrillation



1. **Abstract**

2.
3. *Objective.* In cross-sectional studies, atrial fibrillation (AF) is common in depressed pa-
4. tients, but whether AF causes depression is unclear. We assessed whether AF increases the
5. risk of incident late-life depression.
6. *Methods.* In 4,750 elderly persons from the Rotterdam Study, detailed information on the
7. occurrence of AF and depression was collected between 1993 and 2005. AF was identified
8. by electrocardiography. We categorized depressive episodes as clinically relevant depressive
9. symptoms or as depressive syndromes including DSM-IV defined depressive disorders.
10. We calculated hazard ratios with multivariate Cox regression.
11. *Results.* AF was not associated with an increased risk of depressive symptoms and syn-
12. dromes combined. It was associated with depressive syndromes (HR 1.63; 95% CI 1.04-
13. 2.55) when adjusted for age and sex, but this association lost statistical significance when
14. adjusted for all confounders (HR 1.49; 95% CI 0.94-2.37).
15. *Conclusions.* In this prospective study, AF was not an independent risk factor for incident
16. late-life depression.
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1. Objective

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3. Depressive symptoms occur frequently in the elderly, and even more frequently in patients
4. with atrial fibrillation (AF), the most common cardiac arrhythmia. In a study among
5. 101 patients with AF, 38% had depressive symptoms, which typically had persisted more
6. than 6 months.(1) Also, patients with major depression have AF and related conductive
7. abnormalities on electrocardiography (ECG) more often than healthy controls.(2-4)

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

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16.

17. Methods

18.

19. Setting

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

25.

26. Study population

27. During the second visit, the baseline of the current analysis, 5,769 participants were
28. screened for depressive symptoms. Participants filled out either the validated Dutch ver-
29. sion of the Center for Epidemiologic Studies Depression Scale (CES-D) or the validated
30. Dutch version of the Hospital Anxiety and Depression Scale (HADS-D). A score of 16 or
31. higher out of 60 on the CES-D and 9 or higher out of 21 on the HADS-D was considered
32. screen-positive.(7) At baseline, we excluded 549 persons with depressive symptoms, 105
33. with dementia, 9 with bipolar disorder, 2 who were lost to follow-up directly after screen-
34. ing, and 354 persons with unknown AF status. This resulted in a study population of
35. 4,750 persons, who were free of depression at baseline.

36.

37. Assessment of incident depression

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

1. examination during follow-up visits consisted of a screening with the CES-D, and in the
2. screen-positive participants a semi-structured interview performed by a trained clinician
3. (Schedules for Clinical Assessment in Neuropsychiatry). The self-reported history of de-
4. pression, solicited during the visits, included standardized questions to ascertain whether
5. and when participants had had a depressive episode, and if they had been treated. To
6. continuously monitor incidence of depression throughout follow-up, trained research-
7. assistants scrutinized the medical records of the general practitioners (GPs) and copied the
8. information about a potential depression. Two research physicians independently assessed
9. this information according to a predefined protocol, and discussed discordant assessments.
10. We categorized the depressive episodes into (1) depressive syndromes, including DSM-
11. defined major depressive disorder and dysthymia, and other depressive syndromes, such
12. as depressions recorded by a GP, self-reported depression for which a health professional
13. had been consulted, and DSM-IV minor depression; or (2) ‘clinically relevant depressive
14. symptoms’, if at least one core symptom of major depression had been reported.
15. We defined the date-of-onset as the day of the first report of symptoms, or the first
16. prescription date of an antidepressant drug, whichever came first.

17.

18. **Assessment of atrial fibrillation (AF)**

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

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

33.

34. **Covariables**

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

39.

1. Statistical analysis

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

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

12.

13.

14. Results

15.

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

21. In our study population, a total of 699 incident depressive episodes occurred during
22. 39,840 person-years. Of these episodes, 388 were depressive syndromes, including 99
23. DSM-defined major depressive disorders and dysthymias. Table 1 presents the risk of
24. incident late-life depression related to AF. AF was not associated with depressive symp-
25. toms and syndromes combined. When adjusting for age and sex only, AF was related
26. to depressive syndromes in the complete sample (HR 1.63; 95% CI 1.04-2.55), as well
27. as the subsample of persons without a history of depression (HR 2.00; 95% CI 1.06-
28.

29. **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
30. Complete sample (n=4,750)				
31. AF, age and sex adjusted	1.21 (0.83-1.75)	.32	1.63 (1.04-2.55)	.03
32. AF, adjusted for all confounders*	1.18 (0.81-1.72)	.40	1.49 (0.94-2.37)	.09
33. Persons without history of depression (n=3,215)				
34. AF, age and sex adjusted	1.51 (0.92-2.49)	.11	2.00 (1.06-3.75)	.03
35. AF, adjusted for all confounders*	1.51 (0.90-2.54)	.12	1.60 (0.81-3.15)	.18

36. *adjusted for baseline age, sex, SES, ADL, history of depression, smoking, hypertension, history of ischemic cardiovascular disease,
37. diabetes,

38. myocardial infarct, heart failure, stroke, transient ischemic attacks, use of antihypertensive medication

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1. 3.75). However, when all confounders were adjusted for, AF was not associated with these
2. outcomes in either the complete sample or the subsample of persons without a history of
3. depression. Moreover, in an additional time-varying analysis, that took changes in AF or
4. confounder status after baseline into account, the risk estimates decreased even more: HR
5. 1.18 (95% CI 0.88-1.57) for depressive symptoms and syndromes combined, and HR
6. 1.25 (95% CI 0.85-1.83) for depressive symptoms only (complete sample).

7.
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9. Discussion

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

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

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

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36. References

37. 1. Thrall G, Lip GY, Carroll D, Lane D. Depression, anxiety, and quality of life in patients with atrial
38. fibrillation. *Chest* 2007;132:1259-1264.

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1. 2. Catipovic-Veselica K, Galic A, Jelic K, et al. Relation between major and minor depression and heart rate, heart-rate variability, and clinical characteristics of patients with acute coronary syndrome. *Psychol Rep* 2007;100:1245-1254.
2. 3. Emul M, Dalkiran M, Samim S, et al. The influences of depression and venlafaxine use at therapeutic doses on atrial conduction. *J Psychopharmacol* 2009;23:163-167.
3. 4. Lyness JM, Caine ED, King DA, Conwell Y, Cox C, Duberstein PR. Cerebrovascular risk factors and depression in older primary care patients: testing a vascular brain disease model of depression. *Am J Geriatr Psychiatry* 1999;7:252-258.
4. 5. Carney RM, Freedland KE, Veith RC. Depression, the autonomic nervous system, and coronary heart disease. *Psychosom Med* 2005;67 Suppl 1:S29-33.
5. 6. Hofman A, Breteler MM, van Duijn CM, et al. The Rotterdam Study: 2010 objectives and design update. *Eur J Epidemiol* 2009;24:553-572.
6. 7. Luijendijk HJ, van den Berg JF, Dekker MJ, et al. Incidence and recurrence of late-life depression. *Arch Gen Psychiatry* 2008;65:1394-1401.
7. 8. Heeringa J, van der Kuip DA, Hofman A, et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart J* 2006;27:949-953.
8. 9. Luijendijk HJ, Stricker BH, Hofman A, Wittteman JC, Tiemeier H. Cerebrovascular risk factors and incident depression in community-dwelling elderly. *Acta Psychiatr Scand* 2008;118:139-148.
9. 10. Lyness JM, King DA, Conwell Y, Cox C, Caine ED. Cerebrovascular risk factors and 1-year depression outcome in older primary care patients. *Am J Psychiatry* 2000;157:1499-1501.
10. 11. Mast BT, Neufeld S, MacNeill SE, Lichtenberg PA. Longitudinal support for the relationship between vascular risk factors and late-life depressive symptoms. *Am J Geriatr Psychiatry* 2004;12:93-101.
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Chapter 5

Beta-blockers



1. **Abstract**

2.

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

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

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

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

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1. Introduction

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

9. The most widely proposed explanation for the relationship between beta-blockers and
10. depression is that the drugs decrease noradrenergic activity in the brain.(3, 4) This suggests
11. that non-selective beta-blockers, blocking beta-2 in addition to beta-1 adrenoceptors, may
12. be more likely to induce depression than selective beta-blockers. Indeed, all beta-blockers
13. that have ever been individually associated with an increased risk of depression are also
14. non-selective: propranolol, oxprenolol, nadolol, sotalol and timolol (2, 5, 6). However,
15. to our knowledge, this hypothesis has been investigated in only one study. This cross-
16. sectional study yielded an odds ratio of 1.8 for DSM-defined major depression (95%CI:
17. 1.1-3.1) for non-selective beta-blockers (7). Another hypothesis is that the affinity with
18. serotonergic (5-HT1A) receptors forms the actual iatrogenic mechanism of action. More-
19. over, independent of the actual mechanism involved, lipophilic beta-blockers may be the
20. most likely candidates for conveying an increased risk of depression because they pass the
21. blood brain barrier most easily. Propranolol and oxprenolol, both lipophilic beta-blockers,
22. have in fact been associated with an increased risk of depression (2, 6).

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

27.

28.

29. Methods

30.

31. Setting

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

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

3.

4. **Study population**

5. The study population consisted of persons at risk for incident depression and was selected
6. as follows. During the second examination round in the Rotterdam Study, the baseline
7. of the current analysis, 5769 participants were screened for depressive symptoms. Partici-
8. pants filled out either the validated Dutch version of the Center for Epidemiologic Studies
9. Depression Scale (CES-D) or the validated Dutch version of the Hospital Anxiety and
10. Depression Scale (HADS)(9, 10). Persons with a score of 16 or higher on the CES-D or
11. 9 or higher on the HADS were considered screen-positive. At baseline, we excluded 549
12. persons with depressive symptoms, 105 persons with dementia, 9 persons with bipolar
13. disorder, and 2 persons lost to follow-up directly after screening. This resulted in a study
14. population of 5104 persons free of depression at baseline.

15.

16. **Assessment of incident depression**

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

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

39.

1. **Exposure definition**

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

19.

20. **Covariates**

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

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

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

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

8.

9. **Statistical analysis**

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

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

31.

32.

33. **Results**

34.

35. We identified 736 new-onset depressive episodes in 42,145 person-years, of which 329
36. were episodes of depressive symptoms, and 407 depressive syndromes. Table 1 presents the
37. baseline characteristics of the study sample. The average age was 70 years with a range of 56
38. to 101 years and 58 % of the participants were female. The most prevalent cardiovascular
39. 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 metoprolol (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

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

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

Exposure	Depressive symptoms				Depressive syndromes			
	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)	-		-		-		-	
use during 1-90 days	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 > 90 day	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

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

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

30. Due to collinearity between lipid-solubility and serotonergic receptor affinity, we could not
 31. fit one statistical model with all three groups of beta-blockers in order to test whether one group
 32. in particular accounted for the increase in the risk of depressive symptoms. However, non-selec-
 33. tive, highly lipid-soluble beta-blockers carried a risk of depressive symptoms in the first 90 days
 34. of use (HR 3.45; 95% CI 1.08-11.0) similar that of all highly lipid-soluble beta-blockers (HR
 35. 3.31; 95% CI 1.03-10.6). Non-selective beta-blockers with low to moderate lipid-solubility
 36. were not associated with an increased risk of depressive symptoms in the first 90 days of use
 37. (HR 1.70; 95% CI 0.73-3.96). When we restricted exposure further to highly lipid-soluble,
 38. non-selective beta-blockers with serotonergic affinity, that is propranolol and alprenolol, the
 39. risk of depressive symptoms in the first 90 days of use was 3.81 (95% CI 1.19-12.2).

1. Discussion

2.

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

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

1. finity were not significantly associated with incident depression in our study. On the other
2. hand, non-selective (beta-2 blocking) beta-blockers were associated with an increased risk
3. of incident depression. An odds ratio of 1.8 for DSM-defined major depression (95%CI:
4. 1.1-3.1) has been found before in a cross-sectional study (7). In animal research, the
5. beta-1 and beta-2 adrenoceptor antagonists alprenolol, pindolol, propranolol, and sotalol
6. were found to block the action of nortriptyline, as shown by Yalcin et al in a study in
7. mice (34). Conversely, salbutamol, a beta-2 adrenergic stimulant had been found to be
8. as effective as clomipramine in a small trial with depressed inpatients (35). Positive cor-
9. relations were also observed between the number of lymphocyte beta-adrenoceptors and
10. the rating on the Beck and Hamilton depression questionnaires in patients with major
11. depressive disorder (36). Yet, we also found that non-selective beta-blockers with high
12. lipid-solubility, i.e. propranolol, penbutolol and alprenolol in our study population (see
13. table 2), have a similar risk of depressive symptoms as the whole group of highly lipid-
14. soluble beta-blockers. This suggests that the increased risk that we found for non-selective
15. beta-blockers may be explained by the fact that many of these beta-blockers are highly
16. lipid-soluble. Moreover, non-selective beta-blockers with low to moderate lipid-solubility
17. were not related to depression in our study. When we studied highly lipid-soluble beta-
18. blockers with serotonergic affinity, in our study consisting of alprenolol and in most users
19. propranolol, the risk was similar to that of the whole group of highly lipid-soluble beta-
20. blockers as well. Given the abundance of studies that have implicated a depressogenic
21. effect of propranolol, it is possible that propranolol itself explains our findings.

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

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

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

7. References

8. 1. Waal HJ. Propranolol-induced depression. *Br Med J* 1967;2:50.
9. 2. Steffensmeier JJ, Ernst ME, Kelly M, Hartz AJ. Do randomized controlled trials always trump case
 10. reports? A second look at propranolol and depression. *Pharmacotherapy* 2006;26:162-167.
11. 3. Ried LD, McFarland BH, Johnson RE, Brody KK. Beta-blockers and depression: the more the murkier?
 12. *Ann Pharmacother* 1998;32:699-708.
13. 4. Griffin SJ, Friedman MJ. Depressive symptoms in propranolol users. *J Clin Psychiatry* 1986;47:453-
 14. 457.
15. 5. Julian DG, Prescott RJ, Jackson FS, Szekely P. Controlled trial of sotalol for one year after myocardial
 16. infarction. *Lancet* 1982;1:1142-1147.
17. 6. Thiessen BQ, Wallace SM, Blackburn JL, Wilson TW, Bergman U. Increased prescribing of antidepressants
 18. subsequent to beta-blocker therapy. *Arch Intern Med* 1990;150:2286-2290.
19. 7. Dhondt TD, Beekman AT, Deeg DJ, Van Tilburg W. Iatrogenic depression in the elderly. Results from
 20. a community-based study in the Netherlands. *Soc Psychiatry Psychiatr Epidemiol* 2002;37:393-398.
21. 8. Hofman A, Breteler MM, van Duijn CM, et al. The Rotterdam Study: 2010 objectives and design
 22. update. *Eur J Epidemiol* 2009;24:553-572.
23. 9. Beekman AT, Deeg DJ, Van Limbeek J, Braam AW, De Vries MZ, Van Tilburg W. Criterion validity
 24. of the Center for Epidemiologic Studies Depression scale (CES-D): results from a community-based
 25. sample of older subjects in The Netherlands. *Psychol Med* 1997;27:231-235.
26. 10. Herrmann C. International experiences with the Hospital Anxiety and Depression Scale--a review of
 27. validation data and clinical results. *J Psychosom Res* 1997;42:17-41.
28. 11. Luijendijk HJ, van den Berg JF, Dekker MJ, et al. Incidence and recurrence of late-life depression. *Arch*
 29. *Gen Psychiatry* 2008;65:1394-1401.
30. 12. WHO. SCAN Schedules for Clinical Assessment in Neuropsychiatry, Version 2.1., 2nd ed. Geneva:
 31. World Health Organisation, 1997.
32. 13. APA. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR). Washington DC: APA,
 33. 2000.
34. 14. Mannhold R. The impact of lipophilicity in drug research: a case report on beta-blockers. *Mini Rev Med*
 35. *Chem* 2005;5:197-205.
36. 15. Nagatomo T, Hosohata Y, Ohnuki T, Suzuki J. [Pharmacological characteristics of the long-acting beta-
 37. blocker "bopindolol"]. *Nippon Yakurigaku Zasshi* 1997;109:1-12.
38. 16. Peroutka SJ. Antimigraine drug interactions with serotonin receptor subtypes in human brain. *Ann*
 39. *Neurol* 1988;23:500-504.
17. Rabiner EA, Gunn RN, Castro ME, et al. beta-blocker binding to human 5-HT(1A) receptors in vivo
 and in vitro: implications for antidepressant therapy. *Neuropsychopharmacology* 2000;23:285-293.
18. Bloom M. Measurement of the socioeconomic status of the aged: new thoughts on an old subject.
Gerontologist 1972;12:375-378.

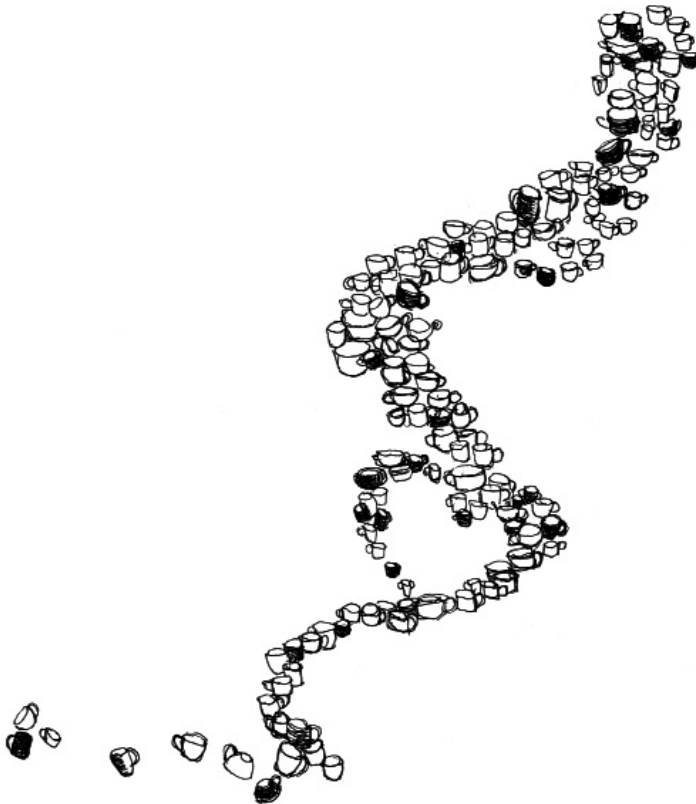
1. 19. Pincus T, Summey JA, Soraci SA, Jr., Wallston KA, Hummon NP. Assessment of patient satisfaction in activities of daily living using a modified Stanford Health Assessment Questionnaire. *Arthritis Rheum* 1983;26:1346-1353.
2. 20. WHO. 1999 World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension. Guidelines Subcommittee. *J Hypertens* 1999;17:151-183.
3. 21. de Bruyne MC, Mosterd A, Hoes AW, et al. Prevalence, determinants, and misclassification of myocardial infarction in the elderly. *Epidemiology* 1997;8:495-500.
4. 22. Bleumink GS, Knetsch AM, Sturkenboom MC, et al. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure The Rotterdam Study. *Eur Heart J* 2004;25:1614-1619.
5. 23. van Durme YM, Verhamme KM, Stijnen T, et al. Prevalence, incidence, and lifetime risk for the development of COPD in the elderly: the Rotterdam study. *Chest* 2009;135:368-377.
6. 24. Bright RA, Everitt DE. Beta-blockers and depression. Evidence against an association. *Jama* 1992;267:1783-1787.
7. 25. Gerstman BB, Jolson HM, Bauer M, Cho P, Livingston JM, Platt R. The incidence of depression in new users of beta-blockers and selected antihypertensives. *J Clin Epidemiol* 1996;49:809-815.
8. 26. Hallas J. Evidence of depression provoked by cardiovascular medication: a prescription sequence symmetry analysis. *Epidemiology* 1996;7:478-484.
9. 27. Ko DT, Hebert PR, Coffey CS, Sedrakyan A, Curtis JP, Krumholz HM. Beta-blocker therapy and symptoms of depression, fatigue, and sexual dysfunction. *Jama* 2002;288:351-357.
10. 28. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30:239-245.
11. 29. Sorensen HT, Mellemkjaer L, Olsen JH. Risk of suicide in users of beta-adrenoceptor blockers, calcium channel blockers and angiotensin converting enzyme inhibitors. *Br J Clin Pharmacol* 2001;52:313-318.
12. 30. Beck CA, Patten SB, Williams JV, et al. Antidepressant utilization in Canada. *Soc Psychiatry Psychiatr Epidemiol* 2005;40:799-807.
13. 31. Gardarsdottir H, Heerdink ER, van Dijk L, Egberts AC. Indications for antidepressant drug prescribing in general practice in the Netherlands. *J Affect Disord* 2007;98:109-115.
14. 32. Ohayon MM, Lader MH. Use of psychotropic medication in the general population of France, Germany, Italy, and the United Kingdom. *J Clin Psychiatry* 2002;63:817-825.
15. 33. Ornstein S, Stuart G, Jenkins R. Depression diagnoses and antidepressant use in primary care practices: a study from the Practice Partner Research Network (PPRNet). *J Fam Pract* 2000;49:68-72.
16. 34. Yalcin I, Choucair-Jaafar N, Benbouzid M, et al. beta(2)-adrenoceptors are critical for antidepressant treatment of neuropathic pain. *Ann Neurol* 2009;65:218-225.
17. 35. Lecrubier Y, Puech AJ, Jouvent R, Simon P, Widlocher D. A beta adrenergic stimulant (salbutamol) versus clomipramine in depression: a controlled study. *Br J Psychiatry* 1980;136:354-358.
18. 36. Carstens ME, Engelbrecht AH, Russell VA, et al. Beta-adrenoceptors on lymphocytes of patients with major depressive disorder. *Psychiatry Res* 1987;20:239-248.
19. 37. Patten SB, Barbui C. Drug-induced depression: a systematic review to inform clinical practice. *Psychother Psychosom* 2004;73:207-215.
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Part III

**Vascular brain disease and
late-life depression**

Chapter 6

Cerebrovascular risk factors



1. **Abstract**

2.

3. *Introduction.* The ‘vascular depression’ hypothesis suggests that late-life depression results
4. from vascular brain damage. We studied the longitudinal association between cerebrovas-
5. cular risk factors and incident depression in a large population-based study.

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

9. *Results.* Only current smoking and anti-hypertensive drug use were independently associ-
10. ated with incident depressive symptoms. Diabetes mellitus, and the Framingham stroke
11. risk score were related to incident depressive disorder. No relation with depression was
12. observed for cholesterol, diastolic and systolic blood pressure, history of cardiovascular
13. disease, atrial fibrillation, left ventricular hypertrophy, or the use of statins and antico-
14. agulants.

15. *Conclusion.* These results moderately support the ‘vascular depression’ hypothesis.

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1. Introduction

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

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

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

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

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31. Methods

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33. Setting

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

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

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

17.

18. **Study population**

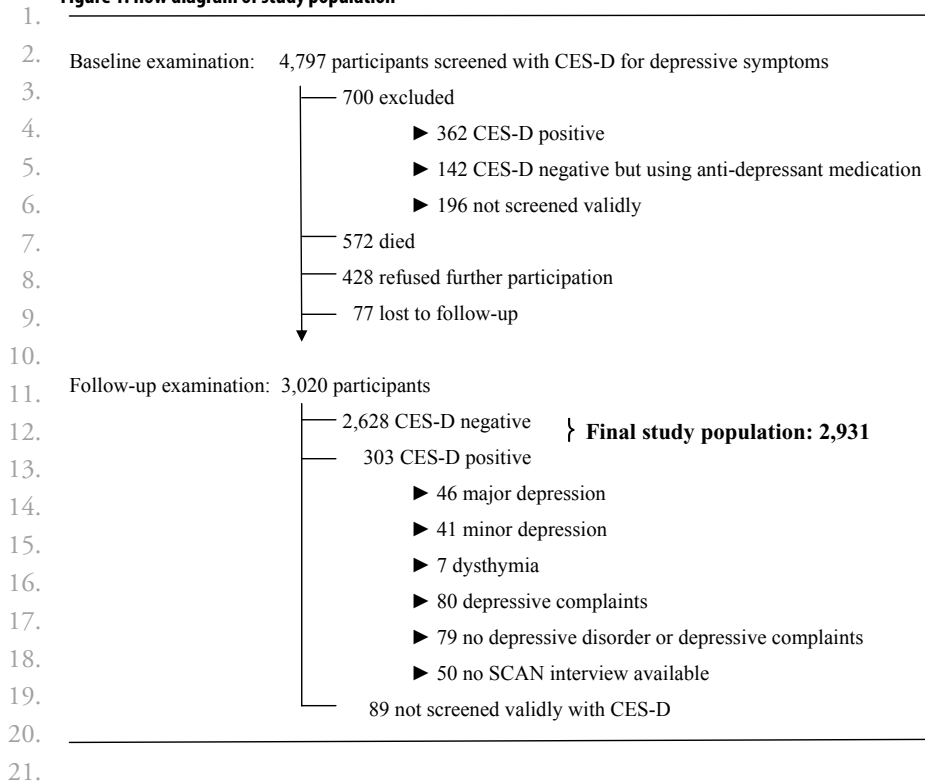
19. Of 5,990 invited participants, 4,797 people took part in the baseline examination (80%).
20. We excluded 362 participants with depressive symptoms and 196 participants who did
21. not answer enough items of the depression screening instrument to calculate a valid score
22. (see figure 1). As the use of anti-depressive medication within six months before the in-
23. terview might have influenced the number and severity of reported depressive symptoms,
24. we also excluded the 142 participants who did not report depressive symptoms but used
25. an antidepressant at baseline. After the baseline examination, 572 individuals died, so that
26. 3,525 participants could be invited for the follow-up examination. 3,020 of them took
27. part (86%). Eventually, 2,931 participants provided valid data about depressive symptoms
28. at follow-up and comprise the study sample for the current analysis.

29.

30. **Assessment of depressive symptoms and depressive disorders**

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

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

Figure 1: flow diagram of study population

22. version of the Present State Examination, a semi-structured psychiatric interview included

23. in the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (20). Major and

24. minor depressive disorders as well as dysthymia were classified according to the DSM-IV

25. criteria, with an algorithm based on the item-scores.

26. As explicated above, our study population consisted of participants who were free of

27. depressive symptoms (CES-D <16) at baseline and were at risk of incident depressive

28. symptoms (CES-D ≥ 16) or an incident DSM-IV defined depressive disorder.

29.

30. **Assessment of cerebrovascular risk factors (CVRFs)**

31. We studied the following CVRFs: smoking, diastolic and systolic blood pressure, diabetes

32. mellitus, total and HDL-cholesterol, history of cardiovascular disease, atrial fibrillation,

33. and left ventricular hypertrophy on ECG.

34. Self-reported smoking was categorized into never, former, and current. Blood pressure

35. was measured twice, after a minimum of five minutes rest, in sitting position at the right

36. upper arm using a random zero sphygmomanometer. The average of the two measurements

37. was calculated. The criteria for diabetes mellitus were: fasting plasma glucose level of 7.0

38. mmol/l or over, non-fasting glucose or an oral glucose tolerance test of 11.1 mmol/L or

39.

1. over, or treatment with an antidiabetic medication or diet. Total serum cholesterol and
2. HDL-cholesterol were determined with an automated enzymatic procedure.
3. Angina pectoris and claudicatio intermittens were established with the Rose question-
4. naire. Other 'signs' of coronary insufficiency were a history of coronary artery bypass
5. grafting, and percutaneous transluminal coronary angioplasty. History of myocardial
6. infarction was defined as self-reported myocardial infarction confirmed by a physician,
7. or myocardial infarction on the echocardiography (ECG) made during the centre visit.
8. A diagnosis of heart failure was classified as definite, probable, possible, or unlikely in
9. accordance with the criteria of the European Society of Cardiology (21), and we included
10. only definite and probable cases included in the analysis.

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

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

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

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1. **Assessment of confounders**

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

10.

11. **Data analysis**

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

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

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

1. in order to avoid bias as a result of regression to the mean in CES-D scores. Nor did we
2. adjust for history of depression, as this would eliminate any possible effect of CVRFs on
3. depression in the years prior to baseline.
4. Two-sided p-values of <0.05 were considered statistically significant. For all statistical
5. analyses we used SPSS for Windows, version 13.0.

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8. **Results**

9.

10. After a follow-up of on average five years, there were 303 persons with a positive CES-D
11. score among the 2,931 participants who formed the study population for the analyses
12. relating to depressive symptoms (see flow diagram). 253 of the 303 screen-positive persons
13. received a psychiatric work-up. There were 94 subjects with an incident depressive disorder:
14. 46 persons fulfilled the DSM-IV-criteria for a major depression, 41 those for a minor
15. depression, and 7 those for dysthymia. In 80 participants, no diagnosis of a depressive
16. disorder according to DSM criteria was made using the psychiatric interview due to insuf-
17. ficiently severe depressive symptoms. These 80 persons with 'depressive complaints' and
18. another 50 with no psychiatric work-up were excluded. The analyses relating to depressive
19. disorders were based on the remaining 2,801 participants.

20. Table 1 presents the baseline characteristics of the study sample. The average age was
21. 71 years with a range of 61 to 95 years and 58% of the participants was female. The
22. most prevalent cerebrovascular risk factor was smoking (51% former smoker, 15.6%
23. current smoker). The average 10-year Framingham stroke risk score was 12 in both men
24. and women, which is equivalent to a 10-year probability of stroke of 12.9% and 9.2%,
25. respectively.

26. Table 2 shows the results for the association between CVRFs at baseline and incident
27. depressive symptoms after five years of follow-up. Increasing age ($\beta=0.16$; 95%
28. CI=0.12-0.20), female sex ($\beta=1.60$; 95% CI=1.12-2.09), current smoking ($\beta=1.53$;
29. 95% CI=0.79-2.28), a history of cardiovascular disease ($\beta=0.96$; 95% CI=0.33-1.59),
30. the use of antihypertensives ($\beta=1.14$; 95% CI=0.65-1.64), and the use of antico-
31. agulants ($\beta=0.73$; 95% CI=0.12-1.34) were statistically significantly associated with
32. reporting depressive symptoms at follow-up. The 10-year Framingham stroke risk score
33. was also associated with the occurrence of incident depressive symptoms ($\beta=0.14$; 95%
34. CI=0.07-0.20). In the multivariate model, only increasing age ($\beta=0.10$; 95% CI=0.05-
35. 0.15), female sex ($\beta=1.43$; 95% CI=0.75-2.11), current smoking ($\beta=1.68$; 95%
36. CI=0.83-2.53), and use of anti-hypertensives ($\beta=1.04$; 95% CI=0.42-1.65) remained
37. significantly associated with incident depressive symptoms at follow-up.

38. In a post-hoc analysis of smoking, we examined the association between pack-years and
39. 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

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

6. That antihypertensive drugs may cause depressive disorders was recognized more than
7. 40 years ago (16). Reserpine and methyldopa are established causes of depressive disor-
8. ders. We found that antihypertensive treatment at baseline was associated with depressive
9. symptoms at follow-up. In another community-based study, low diastolic blood pressure
10. at baseline was also associated with incident positive CES-D scores at follow-up (33).
11. These findings suggest that lowering blood pressure itself might be causative, rather than
12. the pharmacological entities. A strong decline of blood pressure may cause serious malaise
13. and lassitude and this may be misclassified as depressive disorder. The fact that certain
14. antihypertensives such as thiazide diuretics and calcium antagonists are less frequently
15. associated with depressive disorder despite their similar effect on blood pressure reduction
16. solves this question only partly (34-39). More detailed studies are needed in which the
17. different kinds of antihypertensive drugs are compared. Clarification of the relationship
18. with depression may have substantial clinical implications.

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

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

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

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

22. Nevertheless, a potential limitation of our study is that selection bias cannot be ruled
23. out. The probability that a participant drops out is higher if he has more vascular health
24. problems at baseline, or if he is depressed at the time of the follow-up examination. We
25. excluded the 50 participants with no psychiatric work-up and this could have introduced
26. bias and might explain some discrepancies between the multivariate models. Another limi-
27. tation is that risk factors that occurred between baseline and follow-up measurement were
28. not captured. This might have led to an underestimation of the associations. In addition,
29. depressive episodes that occurred after baseline and disappeared before the follow-up as-
30. sessment were not identified. As depressive syndromes often have a chronic and recurrent
31. nature (49-52), these episodes most probably consisted of on average shorter episodes.
32. There is some evidence that vascular depression episodes are less likely to be of short
33. duration (4, 5), so that the bias as a result of missing these episodes would have yielded
34. stronger positive associations between vascular risk factors and incident depression. None-
35. theless, the limited number of incident depressive disorders could have been responsible
36. for the negative findings with regard to this outcome. Finally, as we did not fit a separate
37. multivariable model for each individual risk factor, our multivariable models might have
38. been overadjusted with respect to some of these factors, such as atrial fibrillation.
39.

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

References

1. Krishnan KR, McDonald WM. Arteriosclerotic depression. *Med Hypotheses* 1995;44:111-5.
2. Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M. ‘Vascular depression’ hypothesis. *Arch Gen Psychiatry* 1997;54:915-22.
3. Krishnan KR, Hays JC, Blazer DG. MRI-defined vascular depression. *Am J Psychiatry* 1997;154:497-501.
4. Baldwin RC. Is vascular depression a distinct sub-type of depressive disorder? A review of causal evidence. *Int J Geriatr Psychiatry* 2005;20:1-11.
5. Steffens DC, Krishnan KR, Crump C, Burke GL. Cerebrovascular disease and evolution of depressive symptoms in the cardiovascular health study. *Stroke* 2002;33:1636-44.
6. den Heijer T, Launer LJ, Prins ND, van Dijk EJ, Vermeer SE, Hofman A, Koudstaal PJ, Breteler MM. Association between blood pressure, white matter lesions, and atrophy of the medial temporal lobe. *Neurology* 2005;64:263-7.
7. Goldstein LB, Adams R, Alberts MJ, Appel LJ, Brass LM, Bushnell CD, Culebras A, DeGraba TJ, Gorelick PB, Guyton JR, Hart RG, Howard G, Kelly-Hayes M, Nixon JV, Sacco RL, American Heart A, American Stroke Association Stroke C. Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation* 2006;113:e873-923.
8. Longstreth WT, Jr., Arnold AM, Beauchamp NJ, Jr., Manolio TA, Lefkowitz D, Jungreis C, Hirsch CH, O’Leary DH, Furberg CD. Incidence, manifestations, and predictors of worsening white matter on serial cranial magnetic resonance imaging in the elderly: the Cardiovascular Health Study. *Stroke* 2005;36:56-61.
9. Prins ND. Cerebral Small Vessel Disease in Dementia and Depression: A Population-Based MRI Study. Department of Epidemiology & Biostatistics. Rotterdam: Erasmus Medical Center; 2004.
10. Schmidt R, Schmidt H, Kapeller P, Lechner A, Fazekas F. Evolution of white matter lesions. *Cerebrovasc Dis* 2002;13 Suppl 2:16-20.
11. van Dijk EJ, Breteler MM, Schmidt R, Berger K, Nilsson LG, Oudkerk M, Pajak A, Sans S, de Ridder M, Dufouil C, Fuhrer R, Giampaoli S, Launer LJ, Hofman A. The association between blood pressure, hypertension, and cerebral white matter lesions: cardiovascular determinants of dementia study. *Hypertension* 2004;44:625-30.

1. 12. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. *Stroke* 1991;22:312-8.
2. 13. Kim JM, Stewart R, Kim SW, Yang SJ, Shin IS, Yoon JS. Vascular risk factors and incident late-life depression in a Korean population. *Br J Psychiatry* 2006;189:26-30.
3. 14. Holley C, Murrell SA, Mast BT. Psychosocial and vascular risk factors for depression in the elderly. *Am J Geriatr Psychiatry* 2006;14:84-90.
4. 15. Hershman DL, Simonoff PA, Frishman WH, Paston F, Aronson MK. Drug utilization in the old old and how it relates to self-perceived health and all-cause mortality: results from the Bronx Aging Study. *J Am Geriatr Soc* 1995;43:356-60.
5. 16. Beers MH, Passman LJ. Antihypertensive medications and depression. *Drugs* 1990;40:792-9.
6. 17. Steffens DC, McQuoid DR, Krishnan KR. Cholesterol-lowering medication and relapse of depression. *Psychopharmacol Bull* 2003;37:92-8.
7. 18. Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA. Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. *Eur J Epidemiol* 1991;7:403-22.
8. 19. Beekman AT, Deeg DJ, Van Limbeek J, Braam AW, De Vries MZ, Van Tilburg W. Criterion validity of the Center for Epidemiologic Studies Depression scale (CES-D): results from a community-based sample of older subjects in The Netherlands. *Psychol Med* 1997;27:231-5.
9. 20. WHO. SCAN Schedules for Clinical Assessment in Neuropsychiatry, Version 2.1. 2nd ed. Geneva: World Health Organisation; 1997.
10. 21. Remme WJ, Swedberg K. Guidelines for the diagnosis and treatment of chronic heart failure. *Eur Heart J* 2001;22:1527-60.
11. 22. Willems JL, Abreu-Lima C, Arnaud P, van Bommel JH, Brohet C, Degani R, Denis B, Gehring J, Graham I, van Herpen G, et al. The diagnostic performance of computer programs for the interpretation of electrocardiograms. *N Engl J Med* 1991;325:1767-73.
12. 23. Roberts RE, Deleger S, Strawbridge WJ, Kaplan GA. Prospective association between obesity and depression: evidence from the Alameda County Study. *Int J Obes Relat Metab Disord* 2003;27:514-21.
13. 24. Djernes JK. Prevalence and predictors of depression in populations of elderly: a review. *Acta Psychiatr Scand* 2006;113:372-87.
14. 25. Bloom M. Measurement of the socioeconomic status of the aged: new thoughts on an old subject. *Gerontologist* 1972;12:375-8.
15. 26. Pincus T, Summey JA, Soraci SA, Jr., Wallston KA, Hummon NP. Assessment of patient satisfaction in activities of daily living using a modified Stanford Health Assessment Questionnaire. *Arthritis Rheum* 1983;26:1346-53.
16. 27. Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. *J Am Geriatr Soc* 1992;40:922-35.
17. 28. John U, Meyer C, Rumpf HJ, Hapke U. Smoking, nicotine dependence and psychiatric comorbidity--a population-based study including smoking cessation after three years. *Drug Alcohol Depend* 2004;76:287-95.
18. 29. Breslau N. Psychiatric comorbidity of smoking and nicotine dependence. *Behav Genet* 1995;25:95-101.
19. 30. Cervilla J, Prince M, Rabe-Hesketh S. Vascular disease risk factors as determinants of incident depressive symptoms: a prospective community-based study. *Psychol Med* 2004;34:635-41.
20. 31. Klungsoyr O, Nygard JE, Sorensen T, Sandanger I. Cigarette Smoking and Incidence of First Depressive Episode: An 11-Year, Population-based Follow-up Study. *Am J Epidemiol* 2006;163:421-32.
21. 32. Balfour DJ, Ridley DL. The effects of nicotine on neural pathways implicated in depression: a factor in nicotine addiction? *Pharmacol Biochem Behav* 2000;66:79-85.

1. 33. Paterniti S, Verdier-Taillefer MH, Geneste C, Bisserbe JC, Alperovitch A. Low blood pressure and risk of depression in the elderly. A prospective community-based study. *Br J Psychiatry* 2000;176:464-7.
2. 34. Gerstman BB, Jolson HM, Bauer M, Cho P, Livingston JM, Platt R. The incidence of depression in new users of beta-blockers and selected antihypertensives. *J Clin Epidemiol* 1996;49:809-15.
3. 35. Prisant LM, Spruill WJ, Fincham JE, Wade WE, Carr AA, Adams MA. Depression associated with antihypertensive drugs. *J Fam Pract* 1991;33:481-5.
4. 36. Ried LD, Tueth MJ, Handberg E, Kupfer S, Pepine CJ. A Study of Antihypertensive Drugs and Depressive Symptoms (SADD-Sx) in patients treated with a calcium antagonist versus an atenolol hypertension Treatment Strategy in the International Verapamil SR-Trandolapril Study (INVEST). *Psychosom Med* 2005;67:398-406.
5. 37. Thiessen BQ, Wallace SM, Blackburn JL, Wilson TW, Bergman U. Increased prescribing of antidepressants subsequent to beta-blocker therapy. *Arch Intern Med* 1990;150:2286-90.
6. 38. Hallas J. Evidence of depression provoked by cardiovascular medication: a prescription sequence symmetry analysis. *Epidemiology* 1996;7:478-84.
7. 39. Ried LD, McFarland BH, Johnson RE, Brody KK. Beta-blockers and depression: the more the murkier? *Ann Pharmacother* 1998;32:699-708.
8. 40. Palinkas LA, Lee PP, Barrett-Connor E. A prospective study of Type 2 diabetes and depressive symptoms in the elderly: The Rancho Bernardo Study. *Diabet Med* 2004;21:1185-91.
9. 41. Talbot F, Nouwen A. A review of the relationship between depression and diabetes in adults: is there a link? *Diabetes Care* 2000;23:1556-62.
10. 42. Brown LC, Majumdar SR, Newman SC, Johnson JA. Type 2 diabetes does not increase risk of depression. *Cmaj* 2006;175:42-6.
11. 43. de Jonge P, Roy JF, Saz P, Marcos G, Lobo A, Investigators Z. Prevalent and incident depression in community-dwelling elderly persons with diabetes mellitus: results from the ZARADEMP project. *Diabetologia* 2006;49:2627-33.
12. 44. Kessing LV, Nilsson FM, Siersma V, Andersen PK. No increased risk of developing depression in diabetes compared to other chronic illness. *Diabetes Research and Clinical Practice* 2003;62:113-21.
13. 45. Maraldi C, Volpato S, Penninx BW, Yaffe K, Simonsick EM, Strotmeyer ES, Cesari M, Kritchevsky SB, Perry S, Ayonayon HN, Pahor M. Diabetes mellitus, glycemic control, and incident depressive symptoms among 70- to 79-year-old persons: the health, aging, and body composition study. *Arch Intern Med* 2007;167:1137-44.
14. 46. Blazer DG, Burchett BB, Fillenbaum GG. APOE epsilon4 and low cholesterol as risks for depression in a biracial elderly community sample. *Am J Geriatr Psychiatry* 2002;10:515-20.
15. 47. Lyness JM, King DA, Conwell Y, Cox C, Caine ED. Cerebrovascular risk factors and 1-year depression outcome in older primary care patients. *Am J Psychiatry* 2000;157:1499-501.
16. 48. Mast BT, Neufeld S, MacNeill SE, Lichtenberg PA. Longitudinal support for the relationship between vascular risk factors and late-life depressive symptoms. *Am J Geriatr Psychiatry* 2004;12:93-101.
17. 49. Alexopoulos GS, Young RC, Abrams RC, Meyers B, Shamoian CA. Chronicity and relapse in geriatric depression. *Biol Psychiatry* 1989;26:551-64.
18. 50. Cole MG, Bellavance F, Mansour A. Prognosis of depression in elderly community and primary care populations: a systematic review and meta-analysis. *Am J Psychiatry* 1999;156:1182-9.
19. 51. Kohn R, Epstein-Lubow G. Course and outcomes of depression in the elderly. *Curr Psychiatry Rep* 2006;8:34-40.
20. 52. Palsson S, Skoog I. The epidemiology of affective disorders in the elderly: a review. *Int Clin Psychopharmacol* 1997;12 Suppl 7:S3-13.

Chapter 7

Retinal vascular calibers



1. **Abstract**
- 2.
3. *Objectives.* In order to test the “vascular depression” hypothesis, we investigated whether
4. smaller retinal arteriolar or larger venular calibers, which are markers of cerebral microvas-
5. cular disease, were associated with incident late-life depression.
6. *Methods.* We included 3,605 participants (>55 years) from the population-based Rot-
7. terdam Study, who were free of depression at baseline (1993-1995) and had gradable
8. fundus photographs for retinal vascular caliber measurements. We identified persons with
9. incident depressive symptoms and syndromes using psychiatric interviews during follow-
10. up visits and continuous monitoring. Follow-up was complete until October, 2005.
11. *Results.* After a mean follow-up of 9.0 years, 555 participants developed depressive symp-
12. toms, including 243 with depressive syndrome. Neither smaller arteriolar (age- and sex-
13. adjusted hazard ratio (HR): 1.01; 95%-confidence interval (CI): 0.93-1.10), nor larger
14. venular calibers (HR: 1.02; 95%-CI: 0.94-1.12) were associated with incident depressive
15. symptoms or syndromes.
16. *Conclusions.* Our present data showed no evidence of an association between retinal vascu-
17. lar calibers and incident late-life depression.
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1. Introduction

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

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

22.

23.

24. Methods

25.

26. Study sample

27. The present study was performed as part of the Rotterdam Study, a population-based,
28. cohort study on chronic and disabling diseases in the elderly.(9) A total of 7,983 partici-
29. pants aged 55 years and older and living in one district of Rotterdam agreed to participate.
30. The study was conducted according to the tenets of the Declaration of Helsinki, and the
31. Medical Ethics Committee of the Erasmus Medical Center approved the study protocol. A
32. written informed consent was obtained from all participants. Up till now four visits have
33. taken place during which participants underwent an extensive interview and a physical ex-
34. amination (1989-1993, 1993-1995, 1997-1999, 2002-2004). During the first visit, 5,674
35. participants had gradable fundus photographs and during the second visit, the baseline of
36. the present study, 4,940 participants were screened for depressive symptoms. The study
37. sample for the present study consisted of 3,605 persons who were free of depression at
38. baseline and had gradable fundus transparencies for retinal vascular caliber measurement.
39.

1. **Retinal vascular caliber measurements**

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

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

22.

23. **Assessment of depression**

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

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

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

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

7.

8. **Cardiovascular risk factors**

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

12.

13. **Statistical analyses**

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

21.

22.

23. **Results**

24.

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

29. Neither smaller retinal arteriolar (age- and sex-adjusted HR per SD decrease: 1.01;
30. 95% CI: 0.93-1.10; Wald χ^2 : 0.036; p-value: 0.85) nor larger venular calibers (age- and
31. sex-adjusted HR per SD increase: 1.02; 95% CI: 0.94-1.12; Wald χ^2 : 0.262; p-value:
32. 0.61) were associated with an increased risk of depressive symptoms. The correspond-
33. ing age- and sex-adjusted HR for depressive syndromes were 1.08 (95% CI: 0.94-1.22;
34. Wald χ^2 : 1.242; p-value: 0.27) for arteriolar caliber and 1.00 (95% CI: 0.88-1.14; Wald
35. χ^2 : 0.001; p-value: 0.97) for venular caliber. Categorizing retinal vascular calibers into
36. quartiles did not show a consistent trend towards a higher risk of incident depression.
37. Additional adjustment for other cardiovascular risk factors did not alter the associations.
38. Also, excluding persons with history of depression before the second examination round
39. ($n=1,092$) 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

1. that diabetic patients with major depression ($n=34$; $145.3\mu\text{m}$) had statistically significantly
2. larger retinal arteriolar caliber compared to diabetic patients without depression ($n=27$;
3. $139.2\mu\text{m}$) and healthy persons ($n=38$; $132.6\mu\text{m}$).⁽⁸⁾ However, after additional adjustment
4. for vascular risk factors this trend became non-significant. Findings from these cross-
5. sectional studies are in accordance with the results we found in the current prospective
6. study.

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

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

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

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33. References

34. 1 Kales HC, Maixner DF, Mellow AM: Cerebrovascular disease and late-life depression. *Am J Geriatr*
35. *Psych* 2005; 13:88-98

36. 2 O'Brien JT, Firbank MJ, Krishnan MS, et al. on behalf of the LADIS Group: White matter hyperinten-
37. sities rather than lacunar infarcts are associated with depressive symptoms in older people: the LADIS
38. Study. *Am J Geriatr Psych* 2006; 14:834-841

39.

1. 3 Godin O, Dufouil C, Maillard P, et al : White matter lesions as a predictor of depression in the elderly: The 3C-Dijon Study. *Biol Psychiatry* 2008; 63:663-669
2. 4 Versluis CE, Van der Mast RC, Van Buchem MA, et al: Progression of cerebral white matter lesions is not associated with the development of depressive symptoms in elderly subjects at risk of cardiovascular disease: The PROSPER Study. *Int J Geriatr Psychiatry* 2006; 21:375-381
- 3.
- 4.
5. 5 Rainer MK, Mucke HAM, Zehetmayer S, et al: Data from the VITA Study do not support the concept of vascular depression. *Am J Geriatr Psych* 2006; 14:531-537
- 6.
7. 6 Ikram M.K., E.J. de Jong, E.J. van Dijk, et al: Retinal vessel diameters and cerebral small vessel disease: The Rotterdam Scan Study. *Brain* 2006; 129:182-188
- 8.
9. 7 Sun C, Tikellis G, Klein R, et al: Are microvascular abnormalities in the retina associated with depression symptoms? The Cardiovascular Health Study. *Am J Geriatr Psych* 2007; 15:335-343
10. 8 Nguyen TT, Wong TY, Islam FM, et al: Is depression associated with microvascular disease in patients with type 2 diabetes? *Depress Anxiety* 2008; 25:E158-162
11. 9 Hofman A, Breteler MM, Van Duijn CM, et al: The Rotterdam Study: objectives and design update. *Eur J Epidemiol* 2007; 22:819-829
- 12.
13. 10 Luijckendijk HJ, Van den Berg JF, Dekker MJ, et al: Incidence and recurrence of late-life depression. *Arch Gen Psychiatry* 2008; 65:1394-1401
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Chapter 8

MRI-markers of vascular brain disease



1. **Abstract**

2.

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

6. *Methods.* 479 persons (60-90 years) underwent brain MRI. Brain atrophy, white matter
7. lesions (WML) and brain infarcts reflected vascular brain disease. At baseline (1995-1996)
8. and follow-up examinations we identified persons with depressive symptoms and syn-
9. dromes using CES-D and psychiatric interview. Moreover, medical records were continu-
10. ously monitored to identify incident depression. Follow-up was complete until October
11. 2005.

12. *Results.* At baseline 36 persons had depressive symptoms. Brain atrophy, WML, and in-
13. farcts were associated with presence of depressive symptoms. During follow-up 92 persons
14. developed depressive symptoms, of whom 35 depressive syndrome. There was no associa-
15. tion of any MRI-marker with incident depressive symptoms or syndromes.

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

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1. Introduction

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3. Vascular disease and depression in the elderly are closely related.^{1,2} This has fuelled the

4. 'vascular depression' hypothesis,³ which postulates a vascular basis of late-life depression.⁴⁻⁶

5. With magnetic resonance imaging (MRI) markers of vascular brain disease can be visual-

6. ized, including white matter lesions (WML), brain infarcts, and brain atrophy. Various

7. cross-sectional studies reported an association of several MRI-markers with depression.^{4,7-10}

8. Longitudinal studies thus far only investigated the relationship of WML with depression

9. longitudinally, and found inconsistent results.^{9,11-13} We investigated the relationship of

10. several MRI-markers of subclinical vascular brain disease both cross-sectionally with

11. prevalent depression, and longitudinally with new-onset depression

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14. Methods

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16. Study population

17. This study is based on an age-stratified (60-90 years) sample of 563 participants from the

18. population-based Rotterdam Study,¹⁴ who underwent multi-sequence brain MR-imaging

19. in 1995-1996.¹⁵ The institutional medical-ethics committee approved the study and all

20. participants gave written informed consent. Of the 563 participants, 73 did not com-

21. plete MRI-examination due to claustrophobia or technical reasons, and 4 persons did

22. not undergo psychiatric assessment at baseline. Furthermore, of the eleven persons using

23. anti-depressants at baseline seven had no depressive symptoms. These seven persons were

24. excluded, because we could not determine whether the indication for using this medica-

25. tion was still present. Therefore, a total of 479 persons were available for the analysis.

26.

27. MRI measures at baseline

28. Image acquisition, classification algorithm, and validation steps have been described

29. elsewhere.¹⁵ In summary, we used the k-nearest-neighbor classifier to classify voxels into

30. cerebrospinal fluid, grey matter, normal white matter, and WML. Using non-rigid trans-

31. formation, non-cerebral tissues were stripped. For measurement of lobar and deep central

32. brain volumes, we created an atlas, in which the lobes were labeled according to a slightly

33. modified version of the segmentation protocol as described by Bokde et al.¹⁶ Subsequently,

34. we used validated non-rigid transformation to transform this atlas to each brain. Brain

35. infarcts were rated visually as focal hyperintensities on T2-weighted images, 3 mm in size

36. or larger and with a corresponding prominent hypointensity on T1-weighted images.¹⁵

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1. **Assessment of depression**

2. The assessment of depression has been described elsewhere.¹⁷ At the baseline visit and during
3. three follow-up rounds (1997-1999, 1999-2000, 2000-2001) the Center for Epidemio-
4. logical Studies Depression Scale (CES-D) was used as screening tool with a cut-off of 16.
5. Screen-positive individuals then underwent the Present State Examination¹⁸ to diagnose
6. major depression, dysthymia, and minor depression. The response rate at each of the three
7. follow-up rounds was 95% (437 of the 461 eligible), 81% (336 of 414 eligible), and 81%
8. (309 of 381 eligible). Moreover, medical and pharmacy records of participants (e.g. hospital
9. discharge letter, specialists' reports, and notes of general practitioners) were continuously
10. monitored for depressive episodes and for start of anti-depressants during the follow-up
11. period by automated linkage of the general practitioners' and pharmacists' records with the
12. database. These data ensured virtually complete follow-up among care-seeking participants.
13. Depressive episodes were classified as *depressive symptoms* if persons were CES-D posi-
14. tive; or had at least one core symptom of depression recorded in medical files; or started
15. anti-depressants (without documentation of clinical symptoms). Depressive symptoms
16. were further classified as *depressive syndrome* if persons were diagnosed as suffering from
17. major depression, minor depression, or dysthymia according to the psychiatric interview
18. or medical files. Follow-up for incident depressive symptoms and syndromes was complete
19. until October 1st 2005.

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21. **Covariates**

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

24.

25. **Statistical analysis**

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

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1. Results

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

12.
13. **Table 1 Baseline characteristics of the study population**

14. N	479
15. Age, yr	73.4 (7.8)
16. Women	50%
17. Primary education only	30%
18. MMSE, score	27.7 (2.1)
19. Current smokers	18%
20. Former smokers	54%
21. Systolic blood pressure, mmHg	146 (21)
22. Diastolic blood pressure, mmHg	77 (12)
23. Diabetes mellitus	5.0%
24. Body mass index, kg/m ²	26.2 (3.5)
25. Intima media thickness, mm	0.87 (0.14)
26. MRI markers	
27. Whole brain volume, %ICV	77.4 (3.6)
28. Frontal lobe volume, %ICV	27.4 (1.9)
29. Parietal lobe volume, %ICV	15.8 (1.1)
30. Occipital lobe volume, %ICV	9.0 (0.7)
31. Temporal lobe volume, %ICV	15.5 (0.9)
32. Deep central region*, %ICV	9.7 (0.5)
33. Grey matter, %ICV	46.6 (4.1)
34. Normal white matter, %ICV	29.5 (6.3)
35. Total white matter, %ICV	30.8 (5.7)
36. White matter lesions, %ICV	1.33 (1.51)
37. Brain infarcts	28%

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

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

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

3.

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

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)
7.	Global brain tissue volumes		
8.	Whole brain volume	0.52 (0.31-0.87)	-0.71 (-0.15; 0.03)
9.	Grey matter	0.95 (0.67-1.33)	-0.02 (-0.58; 0.54)
10.	Normal white matter	0.70 (0.46-1.07)	-0.52 (-1.16; 0.13)
11.	Total white matter	0.80 (0.53-1.21)	-0.30 (-0.92; 0.32)
12.	Lobar brain tissue volumes†		
13.	Frontal lobe	0.68 (0.43-1.07)	-0.65 (-1.32; 0.03)
14.	Parietal lobe	0.56 (0.35-0.90)	-0.65 (-1.30; -0.01)
15.	Occipital lobe	0.87 (0.60-1.26)	-0.09 (-0.66; 0.48)
16.	Temporal lobe	0.65 (0.43-0.98)	-0.33 (-0.96; 0.31)
17.	Deep central region	1.08 (0.75-1.53)	0.36 (-0.20; 0.93)
18.	WML volume‡ and brain infarcts		
19.	Global WML	1.56 (0.98-2.46)	0.41 (-0.20; 1.02)
20.	Frontal WML	1.68 (1.07-2.62)	0.45 (-0.14; 1.04)
21.	Parietal WML	1.30 (0.85-1.99)	0.11 (-0.47; 0.68)
22.	Occipital WML	1.45 (0.94-2.23)	0.37 (-0.22; 0.95)
23.	Temporal WML	1.36 (0.89-2.08)	0.38 (-0.22; 0.96)
24.	Deep WML	1.83 (1.13-2.96)	0.72 (0.12; 1.32)
25.	Brain infarcts (yes versus no)	2.35 (1.12-4.91)	0.82 (-0.46; 2.09)

26. 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.

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29. Discussion

30.

31. 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.

32. 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

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

5.

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

7. 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)
10. Global brain tissue volumes		
11. Whole brain volume	1.24 (0.76-2.01)	1.30 (0.67-2.53)
12. Grey matter	0.82 (0.59-1.14)	0.85 (0.53-1.34)
13. Normal white matter	1.34 (0.59-1.14)	1.29 (0.74-2.25)
13. Total white matter	1.32 (0.90-1.93)	1.31 (0.77-2.23)
14. Lobar brain tissue volumes†		
15. Frontal lobe	1.19 (0.77-1.84)	1.35 (0.75-2.45)
16. Parietal lobe	1.06 (0.70-1.58)	1.05 (0.60-1.83)
16. Occipital lobe	1.10 (0.79-1.54)	1.07 (0.67-1.70)
17. Temporal lobe	1.08 (0.72-1.48)	1.04 (0.61-1.80)
18. Deep central region	1.03 (0.72-1.48)	1.05 (0.63-1.75)
19. WML volume‡ and brain infarcts		
20. Global WML	0.76 (0.53-1.08)	0.79 (0.48-1.29)
21. Frontal WML	0.76 (0.55-1.04)	0.78 (0.50-1.22)
21. Parietal WML	0.82 (0.60-1.13)	0.86 (0.55-1.35)
22. Occipital WML	0.89 (0.63-1.27)	0.86 (0.53-1.38)
23. Temporal WML	0.87 (0.61-1.23)	0.92 (0.56-1.52)
23. Deep WML	0.79 (0.55-1.23)	0.89 (0.53-1.50)
24. Brain infarcts (yes versus no)	0.75 (0.33-1.73)	0.83 (0.26-2.70)

25. 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.

27. 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

29.

30. 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

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

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

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21. References

22. 1. Thomas AJ, Kalaria RN, O'Brien JT. Depression and vascular disease: what is the relationship? *J Affect Disord* 2004;79(1-3):81-95.
23. 2. Rao R. Cerebrovascular disease and late life depression: an age old association revisited. *Int J Geriatr Psychiatry* 2000;15(5):419-33.
24. 3. Alexopoulos GS, Meyers BS, Young RC, et al. 'Vascular depression' hypothesis. *Arch Gen Psychiatry* 1997;54(10):915-22.
25. 4. Steffens DC, Helms MJ, Krishnan KR, Burke GL. Cerebrovascular disease and depression symptoms in the cardiovascular health study. *Stroke* 1999;30(10):2159-66.
26. 5. Sheline YI. Neuroimaging studies of mood disorder effects on the brain. *Biol Psychiatry* 2003;54(3):338-52.
27. 6. Thomas AJ, Perry R, Barber R, Kalaria RN, O'Brien JT. Pathologies and pathological mechanisms for white matter hyperintensities in depression. *Ann N Y Acad Sci* 2002;977:333-9.
28. 7. Chen PS, McQuoid DR, Payne ME, Steffens DC. White matter and subcortical gray matter lesion volume changes and late-life depression outcome: a 4-year magnetic resonance imaging study. *Int Psychogeriatr* 2006;18(3):445-56.
29. 8. O'Brien J, Desmond P, Ames D, et al. A magnetic resonance imaging study of white matter lesions in depression and Alzheimer's disease. *Br J Psychiatry* 1996;168(4):477-85.
30. 9. Steffens DC, Krishnan KR, Crump C, Burke GL. Cerebrovascular disease and evolution of depressive symptoms in the cardiovascular health study. *Stroke* 2002;33(6):1636-44.

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1. 10. Almeida OP, Burton EJ, Ferrier N, McKeith IG, O'Brien JT. Depression with late onset is associated with right frontal lobe atrophy. *Psychol Med* 2003;33(4):675-81.
2. 11. Versluis CE, van der Mast RC, van Buchem MA, et al. Progression of cerebral white matter lesions is not associated with development of depressive symptoms in elderly subjects at risk of cardiovascular disease: The PROSPER Study. *Int J Geriatr Psychiatry* 2006;21(4):375-81.
3. 12. Godin O, Dufouil C, Maillard P, et al. White matter lesions as a predictor of depression in the elderly: the 3C-Dijon study. *Biol Psychiatry* 2008;63(7):663-9.
4. 13. Teodorczuk A, O'Brien JT, Firbank MJ, et al. White matter changes and late-life depressive symptoms: longitudinal study. *Br J Psychiatry* 2007;191:212-7.
5. 14. Hofman A, Breteler MM, van Duijn CM, et al. The Rotterdam Study: objectives and design update. *Eur J Epidemiol* 2007;22(11):819-29.
6. 15. Ikram MA, Vrooman HA, Vernooij MW, et al. Brain tissue volumes in the general elderly population. The Rotterdam Scan Study. *Neurobiol Aging* 2008;29(6):882-90.
7. 16. Bokde AL, Teipel SJ, Schwarz R, et al. Reliable manual segmentation of the frontal, parietal, temporal, and occipital lobes on magnetic resonance images of healthy subjects. *Brain Res Brain Res Protoc* 2005;14(3):135-45.
8. 17. Luijckendijk HJ, van den Berg JF, Dekker MJ, et al. Incidence and recurrence of late-life depression. *Arch Gen Psychiatry* 2008;65(12):1394-401.
9. 18. WHO. SCAN Schedules for Clinical Assessment in Neuropsychiatry, Version 2.1. Distribution from Training Centers. 2 ed. Geneva: World Health Organisation, 1997.
10. 19. Sheline YI, Price JL, Vaishnavi SN, et al. Regional white matter hyperintensity burden in automated segmentation distinguishes late-life depressed subjects from comparison subjects matched for vascular risk factors. *Am J Psychiatry* 2008;165(4):524-32.
11. 20. Pantoni L, Garcia JH. Pathogenesis of leukoaraiosis: a review. *Stroke* 1997;28(3):652-9.
12. 21. Scherrer JF, Xian H, Buchholz KK, et al. A twin study of depression symptoms, hypertension, and heart disease in middle-aged men. *Psychosom Med* 2003;65(4):548-57.
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Chapter 9

Transient ischemic attacks



1. Abstract

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

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

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

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

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

20. *Results.* TIAs were significantly associated with the risk of incident depressive disorders and
21. other syndromes (HR 1.68; 95% CI 1.12-2.51), and depressive disorders only (HR 2.42;
22. 95% CI 1.26-4.67). We also found an almost three-fold increased risk of DSM-defined
23. depressive disorders in persons without a history of depression at baseline (HR 2.91; 95%
24. CI 0.96-8.81). In contrast to focal and mixed attacks that comprise TIAs, nonfocal attacks
25. were not related to depression. Including depressive symptoms in the case definition of
26. depression diluted the estimated risk of TIAs.

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

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1. Introduction

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

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

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

39.

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

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10. **Methods**

11.

12. **Setting**

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

23.

24. **Study population**

25. The study population for analysis consisted of persons at risk of incident depression and
26. was selected as follows. During the second examination round, the baseline of the current
27. analysis, 5769 participants were screened for depressive symptoms. Participants filled out
28. either the validated Dutch version of the Center for Epidemiologic Studies Depression
29. Scale (CES-D) or the validated Dutch version of the Hospital Anxiety and Depression
30. Scale (HADS) (26, 27). Persons with a score of 16 or higher on the CES-D or 9 or higher
31. on the HADS were considered screen-positive. At baseline, we excluded 549 persons
32. with depressive symptoms, 105 persons with dementia, 9 persons with bipolar disorder,
33. 2 persons lost to follow-up directly after screening, and 9 persons with unknown stroke
34. status. This resulted in a study population of 5095 persons free of depression at baseline.

35.

36. **Assessment of incident depression**

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

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

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

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

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

22.

23. **Assessment of TIAs and stroke**

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

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

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

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

7.

8. **Covariables**

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

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

30.

31. **Statistical analysis**

32. To study the effect of TIAs on the risk of incident depression, we estimated hazard ratios
33. with Cox proportional hazards analyses. We performed the analyses with three increasingly
34. stringently defined outcomes: time to depressive syndromes and symptoms (categories 1,
35. 2 and 3), depressive syndromes (categories 1 and 2), and depressive disorders (category
36. 1). The exposure of having had a TIA or stroke compared to no cerebrovascular event was
37. entered in the model as a time-varying variable. For each outcome defined above, we fitted
38. a model that included the exposure and the confounders described above. We thus obtain
39. risk estimates that reflect the direct effects of TIAs on the risk of depression, not through

1. stroke. Additionally, in order to further ascertain the chronological relationship between
 2. TIAs and depression, we repeated the models in persons without a history of depression
 3. at baseline.
 4. Finally, we fitted a model in which each first occurrence of a focal, mixed or nonfocal
 5. attack was entered as a time-varying exposure variable, again adjusted for intermediate
 6. stroke and all confounders.
 7. In all analyses, each participant contributed person-years from baseline date until
 8. follow-up ended when a depression occurred, dementia, death, loss-to-follow, or the end
 9. of study period on October 1, 2005. Two-sided p-values of <0.05 were considered statisti-
 10. cally significant. For all statistical analyses we used SPSS for Windows, version 13.0.

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 12.
 13. **Results**

14.
 15. Table 1 presents the baseline characteristics of the study population. The average age was
 16. 70 years with a range of 56 to 101 years and 58 % of the participants were female. The
 17. most prevalent cardiovascular risk factor was history of smoking with 51% former smok-
 18. ers and 17 % current smokers. At baseline, 1641 participants had a history of depression.
 19. One or more TIAs were diagnosed in 86 participants before baseline, and in 239 persons
 20. during follow-up.

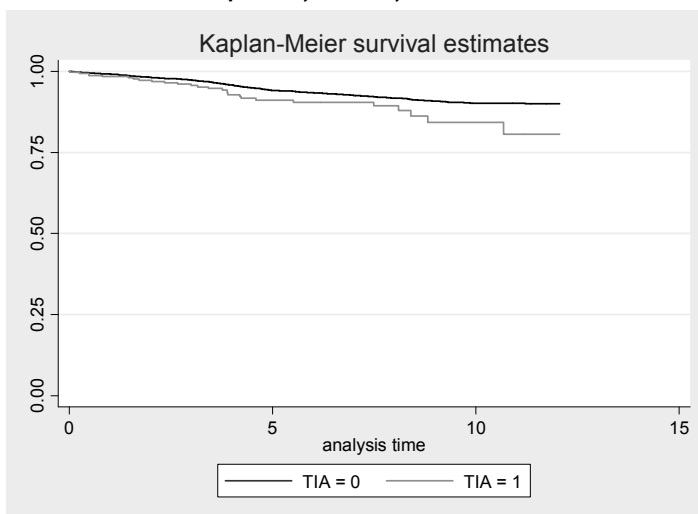
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 22. **Table 1 Baseline characteristics of study population (n=5095)**

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

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 39.

1. In our study population, a total of 736 incident depressions occurred during 42,090
 2. person-years. Of these episodes, 407 were depressive syndromes including 103 DSM-
 3. defined depressive disorders. The mean time between the (first) TIA and a depressive
 4. syndrome was 3.3 years (SD 2.9), counting cases of TIA present at baseline from that time
 5. onward. For incident TIAs only, the mean time to a depressive syndrome was 3.1 years
 6. (SD 2.6). The mean time based on the last (incident) TIA was only a few months short
 7. of the mean time based on first (incident) TIA. Figure 1 shows the Kaplan-Meier survival
 8. curves for depressive syndromes in persons with and without a TIA. After 12 years of
 9. follow-up, twice as many participants with a TIA had developed a depressive syndrome.
 10.

11. **Figure 1 Cumulative survival for incident depressive syndromes by TIA status**



27. Table 2 shows the risk of incident depression associated with TIAs and stroke. TIAs were
 28. more strongly associated with depression the more stringently depression was defined: the
 29. risk of depressive symptoms and syndromes combined was 1.30 (95% CI 0.94-1.80), the
 30. risk of depressive syndromes 1.68 (95% CI 1.12-2.51), and the risk of depressive disorders
 31. 2.42 (95% CI 1.26-4.67). Like TIAs, stroke was also related to depressive syndromes (HR
 32. 1.52; 95% CI 1.01-2.27) and to depressive disorders (HR 3.35; 95% CI 1.82-6.18). The
 33. hazard ratios showed the same pattern in the subsample of persons without a history of
 34. depression at baseline. In fact, the risk of depressive disorders after TIA was as high as 2.91
 35. (95% CI 0.96-8.81).

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

1. depressive disorders (HR 2.17; 95% CI 1.05-4.46). Mixed attacks in particular conveyed
 2. an increased risk of depressive symptoms and syndromes combined (HR 2.25; 95% CI
 3. 1.11-4.55), and depressive syndromes (HR 3.14; 95% CI 1.39-7.12). The risk estimate of
 4. mixed attacks for depressive disorders was not statistically significant (HR 2.88; 95% CI
 5. 0.68-12.3), probably as a result of the small number of cases. In contrast, nonfocal attacks
 6. were not associated with depression.

7.

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

9. Type of attack	10. Depressive syndromes and symptoms (n=736)			11. Depressive syndromes only (n=407)			12. Depressive disorders only (n=103)		
	N	HR (95%CI)	p-value	N	HR (95%CI)	p-value	N	HR (95%CI)	p-value
13. Complete study population (n=5095)									
14. 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
15. 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
16. 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
17. 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
18. Persons without history of depression (n=3454)									
19. 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
20. 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
21. 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
22. 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

23. * adjusted for age, sex, SES, ADL, history of depression, smoking, diastolic and systolic blood pressure, diabetes, history of
 24. cardiovascular disease, chronic heart failure, and use of anti-hypertensives, and censored for stroke; † otherwise known as TIA; ‡
 25. 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

22.

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

24.	25. Depressive syndromes and symptoms (n=736)		26. Depressive syndromes only (n=407)		27. Depressive disorders only (n=103)	
	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
28. 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
29. 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
30. 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

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

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33. Discussion

34.

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

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

12. The association between stroke and subsequent depression has been studied extensively
13. (3, 4, 46, 47). Between 10 and 50% of patients develop depression in the first month
14. after a stroke, and one-year post-stroke the risk is still higher than 30% (1-3). It remains
15. unclear, however, what the direct contribution of the brain lesion is and what the contri-
16. bution of reduced functional status is to the increased risk of depression. To add to the
17. complexity, depression secondary to stroke has been associated with different locations
18. and with decreased catecholamine activity in the injured and uninjured brain structures
19. (2, 4, 48).

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

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

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

9.

10. **Strengths and limitations**

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

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

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

30.

31. **Conclusion**

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

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1. References

2. 1. Chemerinski E, Robinson RG. The neuropsychiatry of stroke. *Psychosomatics* 2000;41(1):5-14.
3. 2. Rao R. Cerebrovascular disease and late life depression: an age old association revisited. *Int J Geriatr Psychiatry* 2000;15(5):419-433.
4. 3. Hackett ML, Yapa C, Parag V, Anderson CS. Frequency of depression after stroke: a systematic review of observational studies. *Stroke* 2005;36(6):1330-1340.
5. 4. Provinciali L, Coccia M. Post-stroke and vascular depression: a critical review. *Neurol Sci* 2002;22(6):417-428.
6. 5. A classification and outline of cerebrovascular diseases. II. *Stroke* 1975;6(5):564-616.
7. 6. Rao R, Jackson S, Howard R. Depression in older people with mild stroke, carotid stenosis and peripheral vascular disease: a comparison with healthy controls. *Int J Geriatr Psychiatry* 2001;16(2):175-183.
8. 7. Hickie I, Simons L, Naismith S, Simons J, McCallum J, Pearson K. Vascular risk to late-life depression: evidence from a longitudinal community study. *Aust N Z J Psychiatry* 2003;37(1):62-65.
9. 8. Arbelaez JJ, Ariyo AA, Crum RM, Fried LP, Ford DE. Depressive symptoms, inflammation, and ischemic stroke in older adults: a prospective analysis in the cardiovascular health study. *J Am Geriatr Soc* 2007;55(11):1825-1830.
10. 9. Larson SL, Owens PL, Ford D, Eaton W. Depressive disorder, dysthymia, and risk of stroke: thirteen-year follow-up from the Baltimore epidemiologic catchment area study. *Stroke* 2001;32(9):1979-1983.
11. 10. Teper E, O'Brien JT. Vascular factors and depression. *Int J Geriatr Psychiatry* 2008;23(10):993-1000.
12. 11. Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M. 'Vascular depression' hypothesis. *Arch Gen Psychiatry* 1997;54(10):915-922.
13. 12. Krishnan KR, McDonald WM. Arteriosclerotic depression. *Med Hypotheses* 1995;44(2):111-115.
14. 13. Krishnan KR, Hays JC, Blazer DG. MRI-defined vascular depression. *Am J Psychiatry* 1997;154(4):497-501.
15. 14. Baldwin RC. Is vascular depression a distinct sub-type of depressive disorder? A review of causal evidence. *Int J Geriatr Psychiatry* 2005;20(1):1-11.
16. 15. Bos MJ, van Rijn MJ, Witteman JC, Hofman A, Koudstaal PJ, Breteler MM. Incidence and prognosis of transient neurological attacks. *Jama* 2007;298(24):2877-2885.
17. 16. Koudstaal PJ, Algra A, Pop GA, Kappelle LJ, van Latum JC, van Gijn J. Risk of cardiac events in atypical transient ischaemic attack or minor stroke. The Dutch TIA Study Group. *Lancet* 1992;340(8820):630-633.
18. 17. Kirshner HS. Vascular dementia: a review of recent evidence for prevention and treatment. *Curr Neurol Neurosci Rep* 2009;9(6):437-442.
19. 18. Evans JG. Transient neurological dysfunction and risk of stroke in an elderly English population: the different significance of vertigo and non-rotatory dizziness. *Age Ageing* 1990;19(1):43-49.
20. 19. Gandolfo C, Caponnetto C, Conti M, Dagnino N, Del Sette M, Primavera A. Prognosis of transient global amnesia: a long-term follow-up study. *Eur Neurol* 1992;32(1):52-57.
21. 20. Hodges JR, Warlow CP. The aetiology of transient global amnesia. A case-control study of 114 cases with prospective follow-up. *Brain* 1990;113 (Pt 3):639-657.
22. 21. Nausieda PA, Sherman IV. Long-term prognosis in transient global amnesia. *Jama* 1979;241(4):392-393.
23. 22. Pantoni L, Bertini E, Lamassa M, Pracucci G, Inzitari D. Clinical features, risk factors, and prognosis in transient global amnesia: a follow-up study. *Eur J Neurol* 2005;12(5):350-356.
24. 23. Tinetti ME, Williams CS, Gill TM. Dizziness among older adults: a possible geriatric syndrome. *Ann Intern Med* 2000;132(5):337-344.

1. 24. Touze E, Varenne O, Chatellier G, Peyrard S, Rothwell PM, Mas JL. Risk of myocardial infarction and vascular death after transient ischemic attack and ischemic stroke: a systematic review and meta-analysis. *Stroke* 2005;36(12):2748-2755.
- 2.
3. 25. Hofman A, Breteler MM, van Duijn CM, Janssen HL, Krestin GP, Kuipers EJ, et al. The Rotterdam Study: 2010 objectives and design update. *Eur J Epidemiol* 2009;24(9):553-572.
- 4.
5. 26. Beekman AT, Deeg DJ, Van Limbeek J, Braam AW, De Vries MZ, Van Tilburg W. Criterion validity of the Center for Epidemiologic Studies Depression scale (CES-D): results from a community-based sample of older subjects in The Netherlands. *Psychol Med* 1997;27(1):231-235.
- 6.
7. 27. Herrmann C. International experiences with the Hospital Anxiety and Depression Scale--a review of validation data and clinical results. *J Psychosom Res* 1997;42(1):17-41.
- 8.
9. 28. Luijckendijk HJ, van den Berg JF, Dekker MJ, van Tuijl HR, Otte W, Smit F, et al. Incidence and recurrence of late-life depression. *Arch Gen Psychiatry* 2008;65(12):1394-1401.
- 10.
11. 29. WHO. SCAN Schedules for Clinical Assessment in Neuropsychiatry, Version 2.1. 2nd ed. Geneva: World Health Organisation, 1997.
- 12.
13. 30. APA. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR). Washington DC: APA, 2000.
- 14.
15. 31. Hollander M, Bots ML, Del Sol AI, Koudstaal PJ, Wittteman JC, Grobbee DE, et al. Carotid plaques increase the risk of stroke and subtypes of cerebral infarction in asymptomatic elderly: the Rotterdam study. *Circulation* 2002;105(24):2872-2877.
- 16.
17. 32. Bloom M. Measurement of the socioeconomic status of the aged: new thoughts on an old subject. *Gerontologist* 1972;12(4):375-378.
- 18.
19. 33. Pincus T, Summey JA, Soraci SA, Jr., Wallston KA, Hummon NP. Assessment of patient satisfaction in activities of daily living using a modified Stanford Health Assessment Questionnaire. *Arthritis Rheum* 1983;26(11):1346-1353.
- 20.
21. 34. Dehghan A, Kardys I, de Maat MP, Uitterlinden AG, Sijbrands EJ, Bootsma AH, et al. Genetic variation, C-reactive protein levels, and incidence of diabetes. *Diabetes* 2007;56(3):872-878.
- 22.
23. 35. de Bruyne MC, Mosterd A, Hoes AW, Kors JA, Kruijssen DA, van Bommel JH, et al. Prevalence, determinants, and misclassification of myocardial infarction in the elderly. *Epidemiology* 1997;8(5):495-500.
- 24.
25. 36. Luijckendijk HJ, Stricker BH, Hofman A, Wittteman JC, Tiemeier H. Cerebrovascular risk factors and incident depression in community-dwelling elderly. *Acta Psychiatr Scand* 2008;118(2):139-148.
- 26.
27. 37. Mast BT, Miles T, Penninx BW, Yaffe K, Rosano C, Satterfield S, et al. Vascular disease and future risk of depressive symptomatology in older adults: findings from the Health, Aging, and Body Composition study. *Biol Psychiatry* 2008;64(4):320-326.
- 28.
29. 38. Holley C, Murrell SA, Mast BT. Psychosocial and vascular risk factors for depression in the elderly. *Am J Geriatr Psychiatry* 2006;14(1):84-90.
- 30.
31. 39. Lyness JM, King DA, Conwell Y, Cox C, Caine ED. Cerebrovascular risk factors and 1-year depression outcome in older primary care patients. *Am J Psychiatry* 2000;157(9):1499-1501.
- 32.
33. 40. Mast BT, Neufeld S, MacNeill SE, Lichtenberg PA. Longitudinal support for the relationship between vascular risk factors and late-life depressive symptoms. *Am J Geriatr Psychiatry* 2004;12(1):93-101.
- 34.
35. 41. Ikram MA, H. J. Luijckendijk, M. W. Vernooij, A. Hofman, W. J. Niessen, A. van der Lugt, H. Tiemeier, M.M.B. Breteler. Vascular brain disease in relation to depression in the elderly. *Epidemiology* (in press).
- 36.
37. 42. Steffens DC, Krishnan KR, Crump C, Burke GL. Cerebrovascular disease and evolution of depressive symptoms in the cardiovascular health study. *Stroke* 2002;33(6):1636-1644.
- 38.
39. 43. Teodorczuk A, O'Brien JT, Firbank MJ, Pantoni L, Poggesi A, Erkinjuntti T, et al. White matter changes and late-life depressive symptoms: longitudinal study. *Br J Psychiatry* 2007;191:212-217.

1. 44. Versluis CE, van der Mast RC, van Buchem MA, Bollen EL, Blauw GJ, Eekhof JA, et al. Progression of cerebral white matter lesions is not associated with development of depressive symptoms in elderly subjects at risk of cardiovascular disease: The PROSPER Study. *Int J Geriatr Psychiatry* 2006;21(4):375-381.
- 2.
- 3.
4. 45. Godin O, Dufouil C, Maillard P, Delcroix N, Mazoyer B, Crivello F, et al. White matter lesions as a predictor of depression in the elderly: the 3C-Dijon study. *Biol Psychiatry* 2008;63(7):663-669.
5. 46. Hackett ML, Anderson CS. Predictors of depression after stroke: a systematic review of observational studies. *Stroke* 2005;36(10):2296-2301.
- 6.
7. 47. Kales HC, Maixner DF, Mellow AM. Cerebrovascular disease and late-life depression. *Am J Geriatr Psychiatry* 2005;13(2):88-98.
- 8.
9. 48. Robinson RG, Chemerinski E, Jorge R. Pathophysiology of secondary depressions in the elderly. *J Geriatr Psychiatry Neurol* 1999;12(3):128-136.
10. 49. Soteriades ES, Evans JC, Larson MG, Chen MH, Chen L, Benjamin EJ, et al. Incidence and prognosis of syncope. *N Engl J Med* 2002;347(12):878-885.
- 11.
12. 50. Aben I, Lodder J, Honig A, Lousberg R, Boreas A, Verhey F. Focal or generalized vascular brain damage and vulnerability to depression after stroke: a 1-year prospective follow-up study. *Int Psychogeriatr* 2006;18(1):19-35.
- 13.
- 14.
15. 51. Koudstaal PJ, Gerritsma JG, van Gijn J. Clinical disagreement on the diagnosis of transient ischemic attack: is the patient or the doctor to blame? *Stroke* 1989;20(2):300-301.
- 16.
17. 52. Tiemeier H, van Dijck W, Hofman A, Witteman JC, Stijnen T, Breteler MM. Relationship between atherosclerosis and late-life depression: the Rotterdam Study. *Arch Gen Psychiatry* 2004;61(4):369-376.
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Part IV

Discussion

Chapter 10

Discussion



1. **Exploring the results**

2.

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

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

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

28.

29. **Vascular heart disease and late-life depression**

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

1. 60s. However, the potential bias introduced by the use of cardiovascular medication has
2. received little attention (12-14).

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

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

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

31.

32. **Vascular brain disease and late-life depression**

33. An abundance of cross-sectional studies has shown an association between cerebrovascular
34. disease and depression (23, 24). These findings have been confirmed in the Rotterdam
35. Study (25, 26). High rates of depression in cerebrovascular disease might be explained by
36. an increased risk of cerebrovascular disease in individuals with depression, by an increased
37. risk of depression in individuals with cerebrovascular disease, or by both. Indeed, depres-
38. sive symptoms have been linked to development of atherosclerosis, incident coronary heart
39.

1. disease, incident stroke and total mortality in apparently healthy elderly persons (27-30).
2. The question remains whether cerebrovascular disease is a risk factor for depression.
3. In 1997, the vascular depression hypothesis was originally formulated as: “cerebrovas-
4. cular disease can predispose, precipitate, or perpetuate a depressive syndrome in older
5. adults” (31). The authors further argued that “direct testing of the vascular depression
6. hypothesis is not possible since the mechanisms of depression are unknown”. In other
7. words, cerebrovascular disease was suggested to catalyze other depressogenic mechanisms.
8. Indeed, it has been shown that stressful life events carry a greater risk of depression in the
9. presence of vascular risk factors (32), and that MRI-visualized brain lesions are associated
10. with persistence and worsening of depressive symptoms over one year (33), but more
11. population-based studies on these topics are still lacking. The majority of prospective
12. studies published to date, like the studies presented in this thesis, assessed whether cere-
13. brovascular disease increased the risk of *incident* depression in the elderly. The implicit
14. hypothesis is that atherosclerotic brain disease has a distinct etiological role in late-life
15. depression (34). A variety of risk factors has been investigated, ranging from individual
16. cerebrovascular risk factors, composite scores of these risk factors, extra cerebrovascular
17. damage, MRI visualized brain damage to clinical cerebrovascular disease. The results of
18. the studies in this thesis and other population-based studies are discussed below.

19. In our study about cerebrovascular risk factors, smoking and the use of antihypertensive
20. drugs were the only individual risk factors related to incident depressive symptoms, and
21. diabetes the only one associated with incident depressive syndromes. All other individual
22. risk factors, i.e. cholesterol, diastolic and systolic blood pressure, a history of cardiovascu-
23. lar disease, atrial fibrillation, left ventricular hypertrophy, or the use of statins and anti-
24. coagulants were not related to either incident depressive symptoms or syndromes. Apart
25. from an ischemic effect on cerebral small vessels, smoking, diabetes and anti-hypertensive
26. drugs have also been hypothesized to cause abnormalities in neurotransmitter metabolism.
27. Moreover, the association between diabetes and depressive disorders may be explained by
28. obesity, a risk factor for diabetes and depression (35), for which we did not adjust. Other
29. population-based studies about cerebrovascular risk factors have yielded similar results
30. (32, 36-44). The only exceptions were that serum total cholesterol, HDL cholesterol,
31. diabetes and history of heart disease were found to be associated with incident depression
32. after two years of follow-up (36, 38). However, the effects of these risk factors were esti-
33. mate in models that were unadjusted for other risk factors, such as smoking and obesity.

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

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

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

10. White matter lesions have always been at the heart of the vascular depression hypothesis
11. (34, 48, 49). In our MR-imaging study, however, there was no association between base-
12. line volume of white matter lesions and incident depressive symptoms or syndromes (50).
13. Moreover, similar results were yielded by a study in an American general population (33).
14. In a French general population, on the hand, higher baseline volume of white matter lesions
15. was related to a higher the risk of developing depressive symptoms during a follow-up of
16. four years (51). An important difference with the two other before mentioned studies was,
17. however, that prevalent and incident dementia had not been taken into account. No re-
18. lationship between progression of white matter lesions and incident depressive symptoms
19. has been found either (52). Another remarkable finding of our imaging study was that
20. brain infarcts were not associated with incident depressive symptoms or syndromes (50).
21. Around 85% of these infarct consisted of so-called silent, or unrecognized, strokes (53).
22. Other structural brain changes, such as cortical atrophy, and hippocampal and amygdalar
23. volumes have not been related to incident depressive symptoms or syndromes in the Rot-
24. terdam Scan Study either (50, 54).

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

33. Overall, the studies in this thesis and those from other population-based settings show
34. that individual cerebrovascular risk factors, composite scores of these risk factors, extra
35. cerebral atherosclerosis, changes in retinal microcirculation, and MRI visualized brain dam-
36. age are not related to incident depression. Only clinical cerebrovascular diseases, such as
37. strokes and transient neurological attacks, seem to be associated with incident depression
38. (24, 55). This is more compatible with a psychological than with a biological role of
39. cerebrovascular disease in the etiology of *incident* late-life depression. Stroke and tran-

1. sient cerebrovascular attacks usually occur out of the blue and may forebode potentially
2. life-threatening re-occurrences. Patients might experience them as a sword of Damocles
3. hovering over their head. Alternatively, functional consequences of cerebrovascular disease
4. may be the causal pathway by which vascular brain lesions are associated with depressive
5. symptomatology. In a meta-analysis, besides stroke severity, physical disability and cogni-
6. tive impairment were risk factors for post-stroke depression (55).
7. Where do all these results leave us? The lack of an association of unsymptomatic
8. cerebrovascular disease and risk factors with the occurrence of new depression suggests
9. that vascular changes observed at the time of the initial assessment have exerted their
10. effect on mood by that time (33). Clearly, longitudinal studies are needed to examine the
11. relationship between incident vascular disease and depression so that the time course can
12. be examined more precisely. In addition, the observation that individuals with unsymp-
13. tomatic cerebrovascular disease who were not depressed at baseline did not tend to become
14. depressed during follow-up raises the question whether they may have protective factors
15. (biological, psychological, or social) that insulate them from depression. Future studies
16. should address this possibility.

17.

18.

19. **Methodological issues**

20.

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

25.

26. **Reliability**

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

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

1. rounds, participants were screened by trained interviewers with the CES-D, which has
2. been validated in elderly populations, and has a sensitivity of 100% and specificity of
3. 88% using a cut-off of 16 (57). Subsequently, experienced and carefully trained clini-
4. cians interviewed screen-positive participants with the Present State Examination (58).
5. However, when depressive episodes are identified during sequential examination rounds
6. only, episodes that have developed and remitted in the interval between rounds may be
7. missed. This will occur especially if the periods between rounds are long, relative to the
8. median duration of episodes.

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

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

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

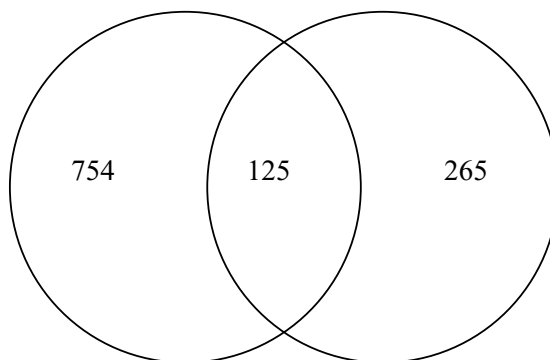
37. The main rationale for using data from other sources, albeit with different diagnostic
38. certainty and reliability, was to ensure that detection of (incident and recurrent) depres-
39. sions was as high as possible. Increasing the number of cases increases the power of a study.

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

18.

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

20.

21. **Psychiatric**
22. **assessments**
23. **(n=879)**24. **Medical**
25. **records**
26. **(n=390)**

27.

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

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

7. Validity

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

16.
 17. Information bias, or measurement bias, is traditionally described as bias resulting from
 18. error in the measurement of the exposure and disease status. To illustrate information
 19. bias in a causal diagram, additional nodes are required: A* for measured exposure, Y*
 20. for measured outcome, and node U for unmeasured variable(s). Figure 2 presents the
 21. three mechanisms by which measurement error may give rise to information bias in a
 22. prospective study (ref).

23.

24. **Figure 2 Information bias in prospective studies**

25. Present (baseline)

Follow-up period

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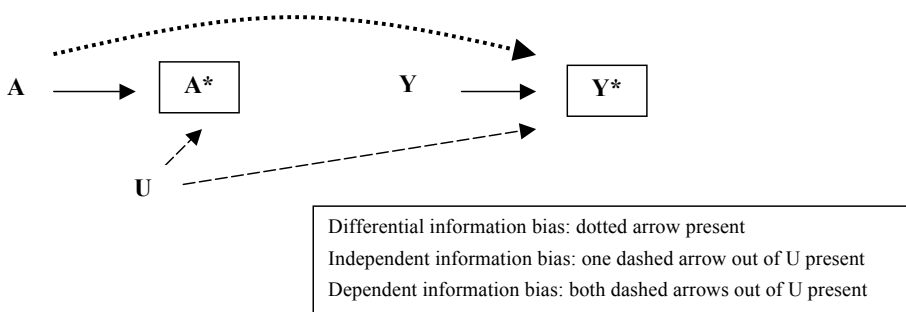
35.

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39.



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.

1. To decrease error in the measurement of the exposure in the studies of this thesis,
2. detailed data was collected about cardiovascular and cerebrovascular disease. Again, data
3. from the examination rounds and medical files were used to establish cases of cardiac
4. and cerebrovascular disease. For the imaging study, an MRI was made in a subgroup of
5. more than 500 participants. The relevance of accurate information on exposure is that
6. information bias (and confounding) is reduced.
7. Although the information on exposure and outcome were collected independently of
8. each other, by different groups of researchers, some differential information bias might
9. still have occurred. If persons with heart failure or transient neurological attack visited
10. their GP or cardiologist more frequently, this will increase the probability that depressions
11. were identified. Thus, analyzing these exposures as time varying variables, like we did, may
12. reduce independent nondifferential information bias on the one hand, but induce some
13. differential information bias on the other. However, given the mean time-lag of more
14. than three years between these diseases and depression, the bias is probably small. Similar
15. differential bias could have occurred in our study about beta-blockers, because physicians
16. have been shown before to err in the direction of falsely calling beta-blocker users cases
17. than users of other drugs (18).
- 18.
19. Confounding occurs when a common cause of the exposure and outcome is not controlled
20. for, even if the exposure has no causal effect on the outcome (see figure 3) (78, 79). This
21. is shown in figure 3 by the presence of the so-called backdoor path (or association) from
22. A through L to Y, independent of an arrow between A and Y.
23. In the studies of this thesis, confounding was minimized by adjusting for factors that
24. were assumed to be common causes of cardio- or cerebrovascular disease as well as depres-
25. sion according to content knowledge. An abundance of information on socio-demographic
26. and health related factors is available in the Rotterdam Study. If the number of baseline
27. confounders was relatively high, the factors that hardly changed the risk estimate were
28. sometimes not included in the analysis in order to preserve power. In addition, given that
29. depression is a risk factor for vascular disease (ref), we rerun the analyses in the subsamples
30. of persons without a history of depression. We also used the time-varying information
31. that was available about the occurrence of confounders such as diabetes and myocardial
32. infarction. Thus, we were able to extensively adjust for confounding.
33. Some residual confounding may still have occurred. We lacked data on thyroid disease
34. related to atrial fibrillation, on severity of heart failure in users of loop-diuretics (we did
35. not have information on New York Heart Association (NYHA) classes I-IV), or cholesterol
36. levels when studying transient neurological attacks. Moreover, in pharmaco-epidemiolog-
37. ical studies confounding by indication may occur. Propranolol, the most commonly used
38. high lipid-soluble beta-blocker, is often prescribed for symptoms that are closely related
39. to depression such as anxiety, alcoholism, and thyroid disease. Finally, overadjustment

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

5.

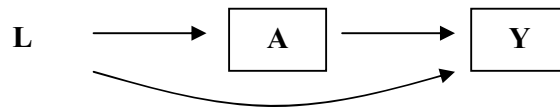
6. **Figure 3 Confounding**

7.

8.

9.

10.



11. 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.

12. Boxes around nodes indicate that the variables that are controlled for in the analysis.

13.

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

17.

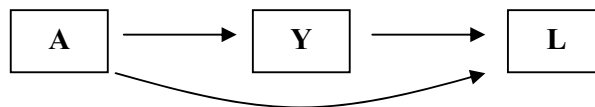
18. **Figure 4 Selection bias**

19.

20.

21.

22.



23. 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

24. around nodes indicate that the variables that are controlled for in the analysis.

25.

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

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

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

4.
5.

6. **Recommendation: from associations to causal effects**

7.

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

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

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

1. 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.

References

1. Lyness JM, King DA, Conwell Y, Cox C, Caine ED. Cerebrovascular risk factors and 1-year depression outcome in older primary care patients. *Am J Psychiatry* 2000;157:1499-1501.
2. Mast BT, Neufeld S, MacNeill SE, Lichtenberg PA. Longitudinal support for the relationship between vascular risk factors and late-life depressive symptoms. *Am J Geriatr Psychiatry* 2004;12:93-101.
3. Rao R, Jackson S, Howard R. Depression in older people with mild stroke, carotid stenosis and peripheral vascular disease: a comparison with healthy controls. *Int J Geriatr Psychiatry* 2001;16:175-183.
4. Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. *J Am Coll Cardiol* 2006;48:1527-1537.
5. Thrall G, Lip GY, Carroll D, Lane D. Depression, anxiety, and quality of life in patients with atrial fibrillation. *Chest* 2007;132:1259-1264.
6. Hofman A, Breteler MM, van Duijn CM, et al. The Rotterdam Study: 2010 objectives and design update. *Eur J Epidemiol* 2009;24:553-572.
7. Ikram MA, Vrooman HA, Vernooij MW, et al. Brain tissue volumes in the general elderly population. The Rotterdam Scan Study. *Neurobiol Aging* 2008;29:882-890.
8. de Jonge P, van den Brink RH, Spijkerman TA, Ormel J. Only incident depressive episodes after myocardial infarction are associated with new cardiovascular events. *J Am Coll Cardiol* 2006;48:2204-2208.
9. Pratt LA, Ford DE, Crum RM, Armenian HK, Gallo JJ, Eaton WW. Depression, psychotropic medication, and risk of myocardial infarction. Prospective data from the Baltimore ECA follow-up. *Circulation* 1996;94:3123-3129.
10. Rowan PJ, Haas D, Campbell JA, Maclean DR, Davidson KW. Depressive symptoms have an independent, gradient risk for coronary heart disease incidence in a random, population-based sample. *Ann Epidemiol* 2005;15:316-320.

1. 11. Carney RM, Freedland KE, Veith RC. Depression, the autonomic nervous system, and coronary heart disease. *Psychosom Med* 2005;67 Suppl 1:S29-33.
2. 12. Beers MH, Passman LJ. Antihypertensive medications and depression. *Drugs* 1990;40:792-799.
3. 13. Hershman DL, Simonoff PA, Frishman WH, Paston F, Aronson MK. Drug utilization in the old old and how it relates to self-perceived health and all-cause mortality: results from the Bronx Aging Study. *J Am Geriatr Soc* 1995;43:356-360.
4. 14. Steffens DC, McQuoid DR, Krishnan KR. Cholesterol-lowering medication and relapse of depression. *Psychopharmacol Bull* 2003;37:92-98.
5. 15. Sorensen HT, Mellemkjaer L, Olsen JH. Risk of suicide in users of beta-adrenoceptor blockers, calcium channel blockers and angiotensin converting enzyme inhibitors. *Br J Clin Pharmacol* 2001;52:313-318.
6. 16. Steffensmeier JJ, Ernst ME, Kelly M, Hartz AJ. Do randomized controlled trials always trump case reports? A second look at propranolol and depression. *Pharmacotherapy* 2006;26:162-167.
7. 17. Thiessen BQ, Wallace SM, Blackburn JL, Wilson TW, Bergman U. Increased prescribing of antidepressants subsequent to beta-blocker therapy. *Arch Intern Med* 1990;150:2286-2290.
8. 18. Gerstman BB, Jolson HM, Bauer M, Cho P, Livingston JM, Platt R. The incidence of depression in new users of beta-blockers and selected antihypertensives. *J Clin Epidemiol* 1996;49:809-815.
9. 19. Hallas J. Evidence of depression provoked by cardiovascular medication: a prescription sequence symmetry analysis. *Epidemiology* 1996;7:478-484.
10. 20. Ko DT, Hebert PR, Coffey CS, Sedrakyan A, Curtis JP, Krumholz HM. Beta-blocker therapy and symptoms of depression, fatigue, and sexual dysfunction. *Jama* 2002;288:351-357.
11. 21. Ried LD, McFarland BH, Johnson RE, Brody KK. Beta-blockers and depression: the more the murkier? *Ann Pharmacother* 1998;32:699-708.
12. 22. Katon W, Lin EH, Kroenke K. The association of depression and anxiety with medical symptom burden in patients with chronic medical illness. *Gen Hosp Psychiatry* 2007;29:147-155.
13. 23. Baldwin RC. Is vascular depression a distinct sub-type of depressive disorder? A review of causal evidence. *Int J Geriatr Psychiatry* 2005;20:1-11.
14. 24. Rao R. Cerebrovascular disease and late life depression: an age old association revisited. *Int J Geriatr Psychiatry* 2000;15:419-433.
15. 25. Tiemeier H, Breteler MM, van Popele NM, Hofman A, Witteman JC. Late-life depression is associated with arterial stiffness: a population-based study. *J Am Geriatr Soc* 2003;51:1105-1110.
16. 26. Tiemeier H, van Dijck W, Hofman A, Witteman JC, Stijnen T, Breteler MM. Relationship between atherosclerosis and late-life depression: the Rotterdam Study. *Arch Gen Psychiatry* 2004;61:369-376.
17. 27. Arbelaez JJ, Ariyo AA, Crum RM, Fried LP, Ford DE. Depressive symptoms, inflammation, and ischemic stroke in older adults: a prospective analysis in the cardiovascular health study. *J Am Geriatr Soc* 2007;55:1825-1830.
18. 28. Ariyo AA, Haan M, Tangen CM, et al. Depressive symptoms and risks of coronary heart disease and mortality in elderly Americans. Cardiovascular Health Study Collaborative Research Group. *Circulation* 2000;102:1773-1779.
19. 29. Faramawi MF, Gustat J, Wildman RP, Rice J, Johnson E, Sherwin R. Relation between depressive symptoms and common carotid artery atherosclerosis in American persons > or =65 years of age. *Am J Cardiol* 2007;99:1610-1613.
20. 30. Larson SL, Owens PL, Ford D, Eaton W. Depressive disorder, dysthymia, and risk of stroke: thirteen-year follow-up from the Baltimore epidemiologic catchment area study. *Stroke* 2001;32:1979-1983.
21. 31. Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M. 'Vascular depression' hypothesis. *Arch Gen Psychiatry* 1997;54:915-922.

32. Holley C, Murrell SA, Mast BT. Psychosocial and vascular risk factors for depression in the elderly. *Am J Geriatr Psychiatry* 2006;14:84-90.
33. Steffens DC, Krishnan KR, Crump C, Burke GL. Cerebrovascular disease and evolution of depressive symptoms in the cardiovascular health study. *Stroke* 2002;33:1636-1644.
34. Krishnan KR, Hays JC, Blazer DG. MRI-defined vascular depression. *Am J Psychiatry* 1997;154:497-501.
35. Roberts RE, Deleger S, Strawbridge WJ, Kaplan GA. Prospective association between obesity and depression: evidence from the Alameda County Study. *Int J Obes Relat Metab Disord* 2003;27:514-521.
36. Kim JM, Stewart R, Kim SW, Yang SJ, Shin IS, Yoon JS. Vascular risk factors and incident late-life depression in a Korean population. *Br J Psychiatry* 2006;189:26-30.
37. Blazer DG, Burchett BB, Fillenbaum GG. APOE epsilon4 and low cholesterol as risks for depression in a biracial elderly community sample. *Am J Geriatr Psychiatry* 2002;10:515-520.
38. Mast BT, Miles T, Penninx BW, et al. Vascular disease and future risk of depressive symptomatology in older adults: findings from the Health, Aging, and Body Composition study. *Biol Psychiatry* 2008;64:320-326.
39. Cervilla J, Prince M, Rabe-Hesketh S. Vascular disease risk factors as determinants of incident depressive symptoms: a prospective community-based study. *Psychol Med* 2004;34:635-641.
40. Palinkas LA, Lee PP, Barrett-Connor E. A prospective study of Type 2 diabetes and depressive symptoms in the elderly: The Rancho Bernardo Study. *Diabet Med* 2004;21:1185-1191.
41. Klungsoyr O, Nygard JF, Sorensen T, Sandanger I. Cigarette Smoking and Incidence of First Depressive Episode: An 11-Year, Population-based Follow-up Study 10.1093/aje/kwj058. *Am. J. Epidemiol.* 2006;163:421-432.
42. Maraldi C, Volpato S, Penninx BW, et al. Diabetes mellitus, glycemic control, and incident depressive symptoms among 70- to 79-year-old persons: the health, aging, and body composition study. *Arch Intern Med* 2007;167:1137-1144.
43. Kessing LV, Nilsson FM, Siersma V, Andersen PK. No increased risk of developing depression in diabetes compared to other chronic illness. *Diabetes Research and Clinical Practice* 2003;62:113-121.
44. Strawbridge WJ, Deleger S, Roberts RE, Kaplan GA. Physical Activity Reduces the Risk of Subsequent Depression for Older Adults 10.1093/aje/kwf047. *Am. J. Epidemiol.* 2002;156:328-334.
45. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. *Stroke* 1991;22:312-318.
46. Vinkers DJ, Stek ML, van der Mast RC, et al. Generalized atherosclerosis, cognitive decline, and depressive symptoms in old age. *Neurology* 2005;65:107-112.
47. Newson RS, Hek, K., Luijendijk, H.J., Hofman, A., Witteman, J.C.M., Tiemeier, H. Atherosclerosis and Incident Depression in Late Life. (submitted).
48. de Groot JC, de Leeuw FE, Oudkerk M, Hofman A, Jolles J, Breteler MM. Cerebral white matter lesions and depressive symptoms in elderly adults. *Arch Gen Psychiatry* 2000;57:1071-1076.
49. Steffens DC, Helms MJ, Krishnan KR, Burke GL. Cerebrovascular disease and depression symptoms in the cardiovascular health study. *Stroke* 1999;30:2159-2166.
50. Ikram MA, H. J. Luijendijk, M. W. Vernooij, A. Hofman, W. J. Niessen, A. van der Lugt, H. Tiemeier, M.M.B. Breteler. Vascular brain disease in relation to depression in the elderly. *Epidemiology in press.*
51. Godin O, Dufouil C, Maillard P, et al. White matter lesions as a predictor of depression in the elderly: the 3C-Dijon study. *Biol Psychiatry* 2008;63:663-669.
52. Versluis CE, van der Mast RC, van Buchem MA, et al. Progression of cerebral white matter lesions is not associated with development of depressive symptoms in elderly subjects at risk of cardiovascular disease: The PROSPER Study. *Int J Geriatr Psychiatry* 2006;21:375-381.

1. 53. Vermeer SE, Koudstaal PJ, Oudkerk M, Hofman A, Breteler MM. Prevalence and risk factors of silent brain infarcts in the population-based Rotterdam Scan Study. *Stroke* 2002;33:21-25.
2. 54. den Heijer T, H. Tiemeier, H.J. Luijendijk, P.J. Koudstaal, A. Hofman, M.M.B. Breteler. Hippocampal and amygdalar volumes and incident depression in late life. (submitted).
3. 55. Hackett ML, Anderson CS. Predictors of depression after stroke: a systematic review of observational studies. *Stroke* 2005;36:2296-2301.
4. 56. Suenkeler IH, Nowak M, Misselwitz B, et al. Timecourse of health-related quality of life as determined 3, 6 and 12 months after stroke. Relationship to neurological deficit, disability and depression. *J Neurol* 2002;249:1160-1167.
5. 57. Beekman AT, Deeg DJ, Van Limbeek J, Braam AW, De Vries MZ, Van Tilburg W. Criterion validity of the Center for Epidemiologic Studies Depression scale (CES-D): results from a community-based sample of older subjects in The Netherlands. *Psychol Med* 1997;27:231-235.
6. 58. WHO. SCAN Schedules for Clinical Assessment in Neuropsychiatry, Version 2.1., 2nd ed. Geneva: World Health Organisation, 1997.
7. 59. Kruijshaar ME, Barendregt J, Vos T, de Graaf R, Spijker J, Andrews G. Lifetime prevalence estimates of major depression: an indirect estimation method and a quantification of recall bias. *Eur J Epidemiol* 2005;20:103-111.
8. 60. Lecrubier Y. Widespread underrecognition and undertreatment of anxiety and mood disorders: results from 3 European studies. *J Clin Psychiatry* 2007;68 Suppl 2:36-41.
9. 61. Simon GE, VonKorff M. Recognition, management, and outcomes of depression in primary care. *Arch Fam Med* 1995;4:99-105.
10. 62. Tylee A, Walters P. Underrecognition of anxiety and mood disorders in primary care: why does the problem exist and what can be done? *J Clin Psychiatry* 2007;68 Suppl 2:27-30.
11. 63. Terluin B, van Hout HP, van Marwijk HW, et al. Reliability and validity of the assessment of depression in general practice: the Short Depression Interview (SDI). *Gen Hosp Psychiatry* 2002;24:396-405.
12. 64. Ohayon MM, Lader MH. Use of psychotropic medication in the general population of France, Germany, Italy, and the United Kingdom. *J Clin Psychiatry* 2002;63:817-825.
13. 65. Patten SB, Esposito E, Carter B. Reasons for antidepressant prescriptions in Canada. *Pharmacoepidemiol Drug Saf* 2007;16:746-752.
14. 66. Beck CA, Patten SB, Williams JV, et al. Antidepressant utilization in Canada. *Soc Psychiatry Psychiatr Epidemiol* 2005;40:799-807.
15. 67. Gardarsdottir H, Heerdink ER, van Dijk L, Egberts AC. Indications for antidepressant drug prescribing in general practice in the Netherlands. *J Affect Disord* 2007;98:109-115.
16. 68. Ornstein S, Stuart G, Jenkins R. Depression diagnoses and antidepressant use in primary care practices: a study from the Practice Partner Research Network (PPRNet). *J Fam Pract* 2000;49:68-72.
17. 69. Alexopoulos GS, Young RC, Abrams RC, Meyers B, Shamoian CA. Chronicity and relapse in geriatric depression. *Biol Psychiatry* 1989;26:551-564.
18. 70. Cole MG, Bellavance F. The prognosis of depression in old age. *Am J Geriatr Psychiatry* 1997;5:4-14.
19. 71. Cole MG, Bellavance F, Mansour A. Prognosis of depression in elderly community and primary care populations: a systematic review and meta-analysis. *Am J Psychiatry* 1999;156:1182-1189.
20. 72. Schoevers RA, Beekman AT, Deeg DJ, Hooijer C, Jonker C, van Tilburg W. The natural history of late-life depression: results from the Amsterdam Study of the Elderly (AMSTEL). *J Affect Disord* 2003;76:5-14.
21. 73. Smits F, Smits N, Schoevers R, Deeg D, Beekman A, Cuijpers P. An epidemiological approach to depression prevention in old age. *Am J Geriatr Psychiatry* 2008;16:444-453.
22. 39.

1. 74. Kohn R, Epstein-Lubow G. Course and outcomes of depression in the elderly. *Curr Psychiatry Rep* 2006;8:34-40.
2. 75. Palsson S, Skoog I. The epidemiology of affective disorders in the elderly: a review. *Int Clin Psychopharmacol* 1997;12 Suppl 7:S3-13.
3. 76. van Weel-Baumgarten EM, Schers HJ, van den Bosch WJ, van den Hoogen HJ, Zitman FG. Long-term follow-up of depression among patients in the community and in family practice settings. A systematic review. *J Fam Pract* 2000;49:1113-1120.
4. 77. Hernan MA. A definition of causal effect for epidemiological research. *J Epidemiol Community Health* 2004;58:265-271.
5. 78. Hernan MA, Hernandez-Diaz S, Werler MM, Mitchell AA. Causal knowledge as a prerequisite for confounding evaluation: an application to birth defects epidemiology. *Am J Epidemiol* 2002;155:176-184.
6. 79. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology* 1999;10:37-48.
7. 80. Hernan MA, Hernandez-Diaz S, Robins JM. A structural approach to selection bias. *Epidemiology* 2004;15:615-625.
8. 81. Hernan MA, Alonso A, Logroschino G. Cigarette smoking and dementia: potential selection bias in the elderly. *Epidemiology* 2008;19:448-450.
9. 82. Rothman KJ, S. Greenland. *Modern Epidemiology*. Philadelphia, PA: Lippincott-Raven Publishers, 1998.
10. 83. Szklo M, FJ. Nieto. *Epidemiology. Beyond the Basics*. Gaithersburg, Maryland: Aspen Publishers, 2000.
11. 84. Hernan MA, Brumback, B, Robins, J. M. Marginal Structural Models to Estimate the Joint Causal Effect of Nonrandomized Treatments. *JASA* 2001;96:440-448.
12. 85. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology* 2000;11:550-560.
13. 86. Sterne JA, Hernan MA, Ledergerber B, et al. Long-term effectiveness of potent antiretroviral therapy in preventing AIDS and death: a prospective cohort study. *Lancet* 2005;366:378-384.
14. 87. Klungel OH, Martens EP, Psaty BM, et al. Methods to assess intended effects of drug treatment in observational studies are reviewed. *J Clin Epidemiol* 2004;57:1223-1231.
15. 88. Smith GD, Ebrahim S. Mendelian randomization: prospects, potentials, and limitations. *Int J Epidemiol* 2004;33:30-42.
16. 89. Hernan MA, Taubman SL. Does obesity shorten life? The importance of well-defined interventions to answer causal questions. *Int J Obes (Lond)* 2008;32 Suppl 3:S8-14.
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Chapter 11

Summary/ Samenvatting



1. **Summary**

2.

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

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

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

39.

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

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

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

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

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1. **Samenvatting**

2.

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

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

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

1. leren, een veel voorkomende hartritmestoornis. Als alleen rekening gehouden werd met
2. verschillen in geslacht en leeftijd tussen de mensen met en zonder boezemfibrilleren leek een
3. verhoogd risico op depressie te bestaan (hoofdstuk 4). Dit verband bleek echter niet meer
4. aanwezig te zijn als ook rekening gehouden werd met verschillen in gezondheidstoestand.
5. Beta-blokkers worden vaak gebruikt bij allerlei hart- en vaatziekten, waaronder hoge
6. bloeddruk, hartaanval, hartfalen, en boezemfibrilleren. Ons onderzoek toonde aan dat
7. gebruik van beta-blokkers in het algemeen niet geassocieerd was met depressie (hoofdstuk
8. 5). Echter, in de eerste drie maanden van gebruik waren beta-blokkers met een hoge
9. vetoplosbaarheid, die relatief gemakkelijk in de hersenen kunnen binnendringen, wel
10. geassocieerd met depressieve symptomen. In onze onderzoekspopulatie betreft dat meestal
11. propranolol, een middel dat meestal gegeven wordt bij angststoornissen, alcoholisme of
12. schildklierandoeningen. Aangezien deze ziekten vaak geassocieerd zijn met depressie, is
13. het de vraag of propranolol een eigenstandig effect heeft op het risico van depressie.
14. Tevens hebben wij de associatie tussen cerebrovasculaire ziekten en depressie onderzocht.
15. Dit sluit aan bij het internationale onderzoek naar de ‘vasculaire depressie’ hypothese die
16. stelt dat depressies bij ouderen eerder optreden als sprake is van cumulatieve vasculaire
17. schade aan het brein. Eerst hebben wij onderzocht of factoren die het risico op vasculaire
18. hersenziekten verhogen geassocieerd zijn met depressie (hoofdstuk 6). Wij vonden dat
19. roken, het gebruik van een medicijn tegen hoge bloeddruk, diabetes en de *Framingham*
20. *stroke risk score*, een risicomaat voor de kans op herseninfarct, geassocieerd waren met het
21. ontwikkelen van depressie. Alle andere factoren, zoals hoge bloeddruk, verhoogd chole-
22. terol, een voorgeschiedenis van vaatziekten van het hart, boezemfibrilleren, of gebruik
23. van cholesterolverlagende of bloedverdunnende medicijnen waren niet geassocieerd met
24. depressie. Vervolgens onderzochten wij meer directe maten voor vaatschade aan het brein.
25. Het volume van de (slag)aders van het netvlies weerspiegelen de toestand van de hersenva-
26. ten. In ons onderzoek was er echter geen relatie tussen deze maat en het ontwikkelen van
27. depressie (hoofdstuk 7). De toestand van de hersenen kan ook gemeten worden met een
28. MRI-scan. Het volume van de grijze en witte stof, als mede de aanwezigheid van hersenin-
29. farcten, vormen een maat voor de vaatschade. In een deel van de onderzoekspopulatie was
30. een dergelijke scan gemaakt. Opnieuw vonden wij geen verband: het volume van de grijze
31. en witte stof, noch herseninfarcten waren geassocieerd met het ontwikkelen van depressie
32. (hoofdstuk 8). Tot slot, onderzochten wij het risico op depressie na een *transient ischemic*
33. *attack*, ook wel TIA. TIAs kunnen optreden als gevolg van langdurige vaatschade van de
34. hersenen. TIAs bleken net als hersenberoertes gepaard te gaan met een verhoogd risico op
35. depressie (hoofdstuk 9).
36. Wij concluderen dat vaatziekten aan hart en hersenen die gepaard gaan met ernstige of
37. bedreigende symptomen zoals hartfalen en TIAs het risico op depressie verhogen (hoofdstuk
38. 10). Ondanks dat in het verleden in dwarsdoorsnede onderzoek vaak een verband gevon-
39. den werd met vaatziekten aan hart en hersenen, vonden wij in ons longitudinale onderzoek

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

2.

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

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11. waarmee je keer op keer nieuwe resultaten en concepthoofdstukken van commentaar
12. voorzag. Eén daarvan was het ‘hoofdpijnhoofdstuk’ over beta-blokkers. Jouw interventies
13. leverde mij als bijwerking maar liefst vier extra concept artikelen op. Beste Henning, ik heb
14. veel van je geleerd over de dagelijkse onderzoekspraktijk, de epidemiologie als wetenschap,
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16. beoordelingen van teksten en tabellen. Er was geen betere manier om te leren hoe ik een
17. artikel langs de reviewers kan krijgen, dan door die te laten lezen door mijn begeleiders.

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25. werkers van het Ergo-centrum, de huisartsen en apothekers van Ommoord, en niet in de
26. laatste plaats de deelnemers van de Rotterdam Study, die belangeloos honderden vragen
27. beantwoordden en allerlei testen ondergingen. Ook de co-auteurs ben ik erkentelijk voor
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33. hun deelname in de grote commissie.

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35. geving belangrijk geweest voor het slagen van mijn promotie-onderzoek. In het bijzonder
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37. dataverzamelaars en later co-auteurs, maar vooral ook enthousiaste en vriendschappelijke
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24. meegekregen van de totstandkoming van dit proefschrift. Laten we dat zo houden: tijd
25. voor een nieuwe reis!
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1. **List of publications**

2.

3. **Papers accepted for publication**

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

7.

8. HJ Luijendijk, BHCh Stricker, A Hofman, JCM Witteman, H Tiemeier. Cerebrovascular
9. risk factors and incident depression in community-dwelling elderly. *Acta Psychiatrica*
10. *Scandinavia* 2008; 118(2):139-48.

11.

12. HJ Luijendijk, H Tiemeier, A Hofman, J Heeringa, BHCh Stricker. Determinants of
13. chronic benzodiazepine use in the elderly: A longitudinal study. *British Journal of Clinical*
14. *Pharmacology* 2008; 65(4): 593-599.

15.

16. HJ Luijendijk, JF van den Berg, MJHJ Dekker, HR van Tuijl, W Otte, F Smit, A Hofman,
17. BHCh Stricker, H Tiemeier. Incidence and recurrence of late-life depression. *Archives of*
18. *General Psychiatry* 2008; 65(12): 1394-1401.

19.

20. M Bijl, HJ Luijendijk, JF van den Berg, LE Visser, RHN van Schaik, A Hofman, AG
21. Vulto, T van Gelder, H Tiemeier, BHCh Stricker. Risk of depression and anxiety in
22. CYP2D6 poor metabolizers. *Pharmacogenomics* 2009; 10(4):541-7.

23.

24. JF van den Berg, HJ Luijendijk, JHM Tulen, A Hofman, A Knuistingh Neven, H Tie-
25. meier. Sleep in depression and anxiety disorders. A population-based study of elderly
26. persons. *Journal of Clinical Psychiatry* 2009; 70(8):1105-13.

27.

28. MA Ikram, HJ Luijendijk, MW Vernooij, A Hofman, WJ Niessen, A van der Lugt, H
29. Tiemeier, MMB Breteler. Vascular brain disease in relation to depression in the elderly.
30. *Epidemiology* (in press)

31.

32. MK Ikram, HJ Luijendijk, A Hofman, PTVM de Jong, JR Vingerling, H Tiemeier.
33. Retinal vascular calibers and risk of late-life depression: the Rotterdam Study. *American*
34. *Journal of Geriatric Psychiatry* (in press)

35.

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

39.

1. **Papers submitted for publication**
2. HJ Luijendijk, H Tiemeier, JF van den Berg, GS Bleumink, A Hofman, BHCh Stricker.
3. Heart failure and incident depression in the elderly (submitted)
- 4.
5. HJ Luijendijk, J Heeringa, A Hofman, JCM Witteman, BHCh Stricker, H Tiemeier.
6. Atrial fibrillation and the risk of incident depression in the elderly (submitted)
- 7.
8. HJ Luijendijk, JF van den Berg, A Hofman, H Tiemeier, BHCh Stricker. Beta-blockers
9. and the risk of incident depression (submitted)
- 10.
11. HJ Luijendijk, BHCh Stricker, RG Wieberdink, PJ Koudstaal, A Hofman, MMB Bre-
12. teler, Henning Tiemeier. Transient ischemic attacks and the risk of developing depression
13. (submitted)
- 14.
15. RS Newson, K Hek, HJ Luijendijk, A Hofman, JCM Witteman, H Tiemeier. Atheroscle-
16. rosis and incident depression in late life (submitted)
- 17.
18. T den Heijer, H Tiemeier, HJ Luijendijk, A Hofman, MMB Breteler. Hippocampal and
19. amygdalar volumes and incident depression in late life (to be submitted)
- 20.
21. HJ Luijendijk, BHCh Stricker, H Tiemeier. Cerebrovascular disease and incident late-life
22. depression: a review of prospective studies (to be submitted)
- 23.
24. **Other publications**
25. HJ Luijendijk and AJB Verkaaik (red). Handboek Sociale Geriatrie. Utrecht: de Tijdst-
26. room, 2006.
- 27.
28. K Brouwer en HJ Luijendijk. Dementie. In: HJ Luijendijk en AJB Verkaaik (red). Hand-
29. boek Sociale Geriatrie. Utrecht: de Tijdstroom, 2006.
- 30.
31. M Stoele, HJ Luijendijk, H.Tiemeier, J Heeringa & H Jansen. Langdurig gebruik van
32. slaap- en kalmeringsmiddelen door ouderen. Een kwantitatieve longitudinale analyse en
33. een kwalitatieve survey onder gebruikers en voorschrijvende artsen in Rotterdam. Rot-
34. terdam: IVO, 2004.
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1. About the author

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

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

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

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