

The long-term impact of rheumatoid arthritis and comorbidity on functioning and mortality



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ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam op gezag van de Rector Magnificus
prof. dr. ir. K.I.J. Maex

ten overstaan van een door het College voor Promoties ingestelde commissie,
in het openbaar te verdedigen in de Agnietenkapel
op vrijdag 15 december 2017, te 14.00 uur
door Joëlle van den Hoek
geboren te Apeldoorn

ISBN 978-94-6332-235-5

Artwork cover: Frederique van Verschuer-Karthus/Studio Karthus
Lay-out: Studio Koen Verbeek design&media
Printing: GVO Drukkers en Vormgevers BV

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The printing of this thesis was financially supported by:
The Academic Medical Center/University of Amsterdam; Pfizer B.V. ,
Reade | Center for Rehabilitation and Rheumatology; The Scientific College Physical
Therapy (WCF) of the Royal Dutch Society for Physical Therapy (KNGF).

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Chapter 1

General introduction

GENERAL INTRODUCTION

This thesis presents the results of a longitudinal study on comorbidity, functioning and mortality in patients with rheumatoid arthritis (RA). In this chapter we discuss the main concepts and focus of the thesis, and we will describe the research themes and the design of our study. At the end an outline of this thesis is given.

Rheumatoid arthritis

RA is a chronic systemic inflammatory autoimmune disease characterized by pain and swelling of multiple joints of the body (1,2). Extra articular and systemic manifestations are also part of the disease (3,4). The global prevalence is 0.24% (2). The disease is more common in women (around twice as many women than men are affected) and in developed countries (2). In the Netherlands RA has a prevalence of 0.88% in women and 0.55% in men (5). RA is associated with emerging comorbidities resulting in substantial impacts on functioning and mortality. Limited information exists on these interrelationships.

Comorbidity

Comorbidity, defined as any additional, coexistent condition in a patient with a particular index disease (6), is highly prevalent in patients with RA. Many patients with RA suffer from somatic comorbidities as well as psychological comorbidity, particularly depression. The prevalence of at least one comorbid condition ranges from 32%-70% at disease onset (7-9). The large variation in reported prevalence rates is probably due to differences in the definition of comorbidity, the selected study population and the measurement of comorbidity. Comorbidity in patients with RA becomes more common with age (10) and disease duration (8,9,11). The prevalence rates of somatic comorbidity and comorbid depression in patients with RA are higher than in the general population (12-15). Somatic comorbidities that are over-presented in patients with RA compared with the general population are: cardiovascular (CV) diseases (9,16-20), diseases of the respiratory system (9,21-24), gastrointestinal diseases (17,24,25) and infections (24,26,27), amongst others. Depression is common in patients with RA and occurs even more often than somatic comorbidity (17). The relationship between RA and comorbidity is complex. Some comorbid conditions are linked to the inflammatory process of RA (like CV diseases) while others occur as a consequence of the use of medication (like infections) (28). Having comorbidity is one of the main risk factors for poor health outcomes like a lower level of functioning

and mortality (29,30). To get more insights into the impact of comorbidity in patients with RA we need to focus on a wide range of comorbidities. Specific comorbidities are expected to have varying effects on functioning and mortality (24,28).

Functioning

RA imposes a considerable burden on both physical functioning and mental functioning. Physical functioning refers to the ability to perform activities of daily functioning. Physical functioning can be measured in a disease specific way: the ability to perform activities that are specifically affected in RA (like reaching or opening a new milk carton) (31). It can also be measured in a more generic way: the ability and satisfaction with activities that are affected in any type of disease (like performing work) (32-34). Mental functioning refers to the psychological state of a patient (35). It is often measured as a component of quality of life and includes psychological distress, emotional problems, social functioning and vitality (34).

Both physical and mental functioning has been reported as being important outcomes in patients with RA (36). Patients with RA show lower levels of physical functioning in comparison to the general population (37,38). Physical functioning in patients with established RA shows a course of slow decline (39). Mental functioning in patients with RA appears also to be lower than in the general population (38). However, the impact of RA on physical functioning is higher than on mental functioning (38).

Given the large impact of RA on physical functioning we will first study in this thesis the long-term physical functioning in patients with RA. The results will provide prognostic information about the course of physical functioning of patients with RA over a long-term followup period. These insights will serve as starting point for the studies addressing the impact of comorbidities on this functioning.

Comorbidity and functioning

Several studies have reported the negative association between somatic comorbidity, comorbid depression, and physical functioning. Somatic comorbidity is associated with worse physical functioning (24) on all domains of physical functioning, independent of disease activity (40,41), and is also associated with a decline in physical functioning over time (30). Comorbid depression is associated with worse physical functioning (42-45), as well as worse mental functioning in patients with RA (42,43). Little is known about the effect of somatic comorbidity on mental functioning. We are not aware of studies investigating the co-occurrence of somatic comorbidity and comorbid depression and the differential impact of somatic comorbidity and comorbid depression on functioning. Furthermore, studies so far investigated the impact of comorbidity on functioning over a period of ≤ 5 years. Little is known about the impact of comorbidity in the longer

term, which is particularly relevant for chronic diseases with a course of slow decline. Only a few studies investigated the effects of specific comorbid conditions on physical functioning. The effects of specific comorbidities on mental functioning have, to our knowledge, not yet been investigated. More knowledge on these associations will help clinicians to estimate the prognosis of individual patients with specific comorbidities and to determine treatment options. Thus, we need to have more knowledge about the impact of a wide range of specific comorbid conditions, both somatic comorbidity and comorbid depression, on long-term physical and mental functioning. More knowledge may contribute to increasing quality of care for patients with RA.

Mortality

Patients with RA have a higher mortality risk than people in the general population. Mortality rates in patients with RA are around 1.5 times higher than that of the general population (46).

Causes of death that are increased in patients with RA in comparison with the general population are CV diseases, respiratory diseases and infections (47-50). In the most recent studies, only a limited number of causes of death were studied (51), the number of patients who died during followup was small, and most data came from studies conducted before 2004 (52,53). Thus, there is a need to study cause of death for a wide range of causes, in a large cohort, using recent mortality data.

In the past decades treatment of RA changed substantially and this might impact on the risk of mortality in patients with RA. The treatment focus is now on tight disease control with much earlier initiation of intensive treatment. From the 1990s high dose treatment with disease-modifying antirheumatic drugs (DMARDs) started and biologicals were applied from 2000 onwards (54). Meta-analyses suggest that DMARDs (particularly methotrexate) reduce CV risk (55). Accumulating observational evidence exists that this also applies for biologicals, particularly the TNF-blockers (56,57). Studies that started around 2000, after the introduction of biologicals, studied time trends in all-cause mortality, but showed contradictory results. Some studies report that the mortality in patients with RA was similar to that of the general population (58,59), while other studies showed that the mortality in patients with RA was higher (60,61) or that the mortality gap with the general population was even increasing (53). Thus, given these conflicting results, there is a need to evaluate the risk of mortality in a large sample of patients with RA, over a long period, using more recent mortality data (62).

Comorbidity and mortality

Comorbidity is one of the most significant predictors for mortality in patients with RA (29). In the literature the high number of comorbidities, the existence of more severe

comorbidities and suboptimal care for comorbidities have been proposed as causes of the higher mortality rate (63). Which specific comorbidities are associated with mortality has been less investigated. Evaluating the relative contribution of specific comorbidities will provide valuable information for clinical practice and the management of patients with RA, because preexisting comorbidities are a possible target of disease management. Thus, there is a need to study for a wide range of comorbid conditions the association with mortality in patients with RA to obtain a more comprehensive view and to provide clinically useful tools for optimizing care.

Cardiovascular mortality

We will particularly focus on CV mortality because the higher mortality rate in patients with RA is mainly attributable to CV diseases (47-50). The higher CV mortality risk in RA is caused both by traditional risk factors (smoking, hypertension and dyslipidaemia), occurring more frequently in patients with RA, and the underlying chronic inflammatory process (64-66). Inflammation plays an important role in atherosclerosis and amplifies some traditional CV risk factors (67-69).

Besides the introduction of tight disease control and the more intensive treatment in the past decades, the importance of CV risk management is widely acknowledged (70). This may have resulted in lower CV mortality risk. However, time trends in CV mortality have been studied less. Demographic as well as clinical and functional variables predict CV mortality (47,50,64,65,71). Until now, the impact of these variables on CV mortality has been studied for each variable separately and not in combination. A EULAR task force for CV risk management noted this unmet need and advocated to study for a broad range of variables the combined contribution (demographic, as well as inflammatory, and traditional risk factors) to CV mortality in patients with RA in large prospective cohort studies (70). Thus, there is a need to study the CV mortality in a clinical cohort of patients with RA over a large period, to study the trend in CV mortality and to explore the contribution of a broad range of predictors to CV mortality in patients with RA.

Research themes

In this thesis we aim to gain more insights into the impact of RA and comorbidity on functioning and mortality. In line with the research needs described above we will address the following research themes:

1. The long-term physical functioning in patients with RA and its associations with somatic comorbidity and comorbid depression.
2. The impact of a wide range of specific somatic comorbidities and comorbid depression on long-term physical and mental functioning in patients with RA.

3. The all-cause mortality, the trend in this mortality, and the cause-specific mortality of patients with RA in comparison with the general population.
4. The impact of somatic comorbidities and comorbid depression on mortality in patients with RA.
5. The CV mortality of patients with RA in comparison with the general population, the trend in this mortality, and the impact of a broad range of predictors.

Study design

In this section we will describe the procedure for the recruitment and the selection of the patients, the response and the measurements that were used for this thesis. The RA+ study started in 1997 and was originally designed to study the health care and health outcomes in a cohort of patients with RA. The original goals were 1) providing insight into the health care for patients with RA, and 2) providing insight into functioning and health related quality of life among patients with RA. Data were collected by means of questionnaires and clinical examination. The results addressing the first aim have been presented in the thesis 'Care for patients with rheumatoid arthritis' by C. Jacobi (72). The results with respect to the second aim have been presented in the thesis 'Clinical and patient reported health outcomes in patients with rheumatoid arthritis' by I. Rupp (73).

Patients for this thesis were recruited in 1997 from Reade, center for rehabilitation and rheumatology (formerly Jan van Breemen Institute), and affiliated outpatient clinics. Patients were randomly selected from strata with different disease duration to guarantee the heterogeneity of the cohort. Patients had to fulfill the following criteria: 1) being diagnosed with RA according to the 1987 revised American College of Rheumatology (ACR) criteria (74) 2) being 16 years of age or older 3) having sufficient knowledge of the Dutch language 4) having visited a rheumatologist in the previous two years.

A flow chart summarizing the response process for the 1251 patients selected in 1997, and studied in this thesis, is shown in figure 1. Of the eligible patients 882 responded to the questionnaire in 1997. Of these patients, 755 (87% of the eligible patients) responded in 1998, 683 (81% of the eligible patients) responded in 1999, 529 (71% of the eligible patients) responded in 2002 and finally 370 (62% of the eligible patients) responded in 2008. Rupp et al. investigated predictors for (non)response in 1997 through a telephone interview (75). Patients who responded to the questionnaire reported less pain and where taking more often additional health care than patients who did not respond. Other variables (like disease activity, disease duration, functioning and comorbidity) were not different in both groups.

The sociodemographic variables included age, sex, marital status and sociodemographic variables. The clinical variables included erythrocyte sedimentation

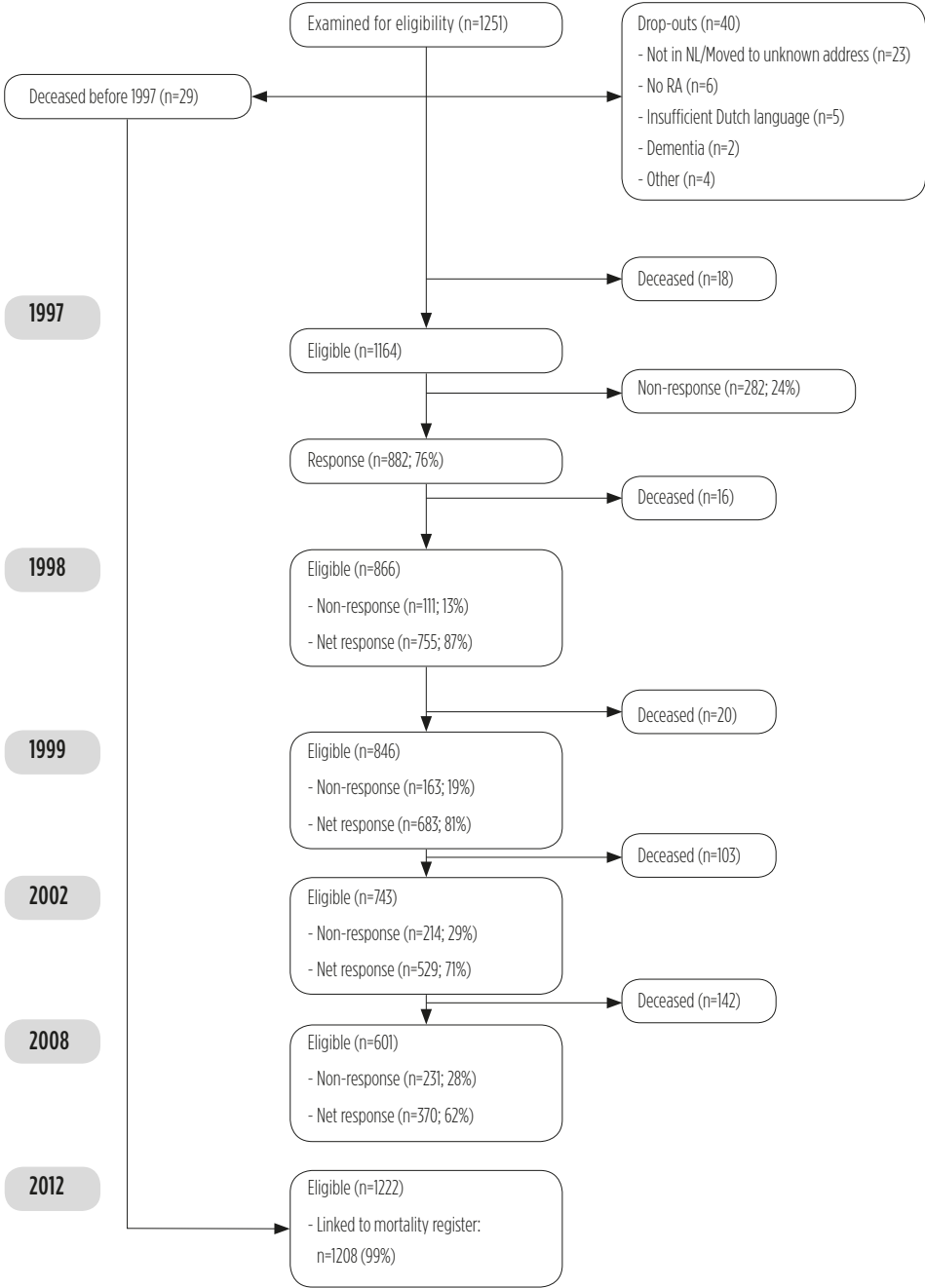


Figure 1. Flow chart of the RA+ study. Net response refers to the number of respondents in relation to the group of patients who responded in 1997 (n=882) and who were still alive at that moment of measurement. Nonresponse is the number of patients who withdrew from the study plus patients who did not respond for one of the measurement moments. NL=The Netherlands.

rate, the DAS 28 joint count, disease duration, rheumatoid factor, pain and comorbidity. Functional variables addressed physical functioning and mental functioning. Physical functioning was measured with the Health Assessment Questionnaire (HAQ) and the physical scales of the Short-Form 36 (SF-36) health survey. Mental functioning was measured with the mental scales of the SF-36. Somatic comorbidity was measured with a self-reported list abstracted from the Health Interview Survey of Statistics Netherlands (76). The list covers 20 chronic conditions, which are prevalent in the Netherlands, and most of them are also prevalent in RA (16, 77). The following 9 categories of somatic comorbidity were created based on the body systems involved (78); 1) circulatory conditions (myocardial infarction or other serious heart disorders, stroke); 2) respiratory conditions (asthma, chronic bronchitis); 3) digestive conditions (disorders of the stomach, disorders of the liver, disorders of the gall bladder, serious disorders of the intestine longer than 3 months); 4) genitourinary conditions (disorders of the kidney, kidney stones, inflammation of the bladder); 5) neurological conditions (migraine, dizziness with falling, epilepsy); 6) musculoskeletal conditions (hernia or chronic back complaints); 7) endocrine, metabolic or nutritional conditions (diabetes mellitus, disorders of the thyroid gland); 8) cancer; 9) a rest category (hypertension, infection of the nasal cavity or frontal sinus, skin conditions). Comorbid depression was measured with the Center for Epidemiologic Depression Scale (CES-D) (79).

For this thesis additional long-term followup data were collected about sociodemographic variables, functioning, quality of life and comorbidity by means of questionnaires in 2008, which enables us to study a relatively longtime horizon. Data about mortality and causes of death were collected through the databank of the Statistics Netherlands throughout 2012. Of the eligible patients who were selected at baseline, 99% could be linked to the databank of the Statistics Netherlands. The Reade/Slotervaart Institutional Review Board approved our study.

Outline of the thesis

This study aims to provide more insight into the long-term impact of RA and a wide range of somatic comorbidities and comorbid depression on functioning and mortality. In chapter 2 we describe the long-term physical functioning and its association with somatic comorbidity and comorbid depression in patients with RA. We elaborate on the impact of comorbidity in chapter 3 by examining the impact of specific comorbid conditions. We describe the impact of a wide range of somatic comorbid conditions and comorbid depression on physical functioning and mental functioning. In chapter 4 we investigate all-cause mortality in patients with RA in comparison with the general Dutch population, the trend in all-cause mortality, and the causes of death. In chapter 5 we describe the results of a study on the association of a wide range of comorbid conditions with mortality. In chapter 6 we examine specifically CV mortality in

patients with RA compared to the general Dutch population, the trend in CV mortality ratio and the contribution of a broad range of predictors to CV mortality. Table 1 presents a schematic overview of the associations that were studied.

Table 1. The Long-term impact of rheumatoid arthritis and comorbidity on functioning and mortality: schematic overview of the studied relationships

Predictor	Outcome	Measurements	Chapter
Rheumatoid Arthritis	Physical functioning	HAQ	2 and 3
		SF-36 PCS	
Comorbidity	Mental functioning	SF-36 MCS	3
	All-cause mortality	Mortality	4 and 5
	Cause-specific mortality	Mortality	4
	Cardiovascular mortality	Mortality	6

HAQ; Health Assessment Questionnaire, SF-36; Short Form-36, PCS; physical component summary score, MCS; mental component summary score.

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Chapter 2

Long-term physical functioning and its association with somatic comorbidity and comorbid depression in patients with established rheumatoid arthritis: a longitudinal study

J van den Hoek, LD Roorda, HC Boshuizen, J van Hees, I Rupp, GJ Tjhuis, J Dekker, GAM van den Bos. Long-term physical functioning and its association with somatic comorbidity and comorbid depression in patients with established rheumatoid arthritis: a longitudinal study. *Arthritis Care and Research (Hoboken)* 2013; 65: 1157-65.

ABSTRACT

Objective. To describe long-term physical functioning and its association with somatic comorbidity and comorbid depression in patients with established rheumatoid arthritis (RA).

Methods. Longitudinal data over a period of 11 years were collected from 882 patients with RA at study inclusion. Patient-reported outcomes were collected in 1997, 1998, 1999, 2002 and 2008. Physical functioning was measured with the Health Assessment Questionnaire and the physical component summary score of the Short Form-36 health survey. Somatic comorbidity was measured by a questionnaire including 12 chronic diseases. Comorbid depression was measured with the Center for Epidemiologic Studies Depression Scale. We distinguished 4 groups of patients based on comorbidity at baseline.

Results. Seventy-two percent of the patients at baseline were women. The mean \pm SD age was 59.3 ± 14.8 years and the median disease duration was 5.0 years (interquartile range 2.0-14.0 years). For the total group of patients with RA, physical functioning improved over time. Patients with somatic comorbidity, comorbid depression or both demonstrated worse physical functioning than patients without comorbidity at all data collection points. Both groups with comorbid depression had the lowest scores. Only patients with both somatic comorbidity and comorbid depression showed significantly less improvement in physical functioning over time.

Conclusion. Both somatic comorbidity and comorbid depression were negatively associated with physical functioning during an 11-year followup period. Furthermore, their combination seems to be especially detrimental to physical functioning over time. These results emphasize the need to take somatic comorbidity and comorbid depression into account in the screening and treatment of patients with RA.

INTRODUCTION

Comorbidity, defined as any additional, coexistent condition in a patient with a particular index disease (1), is highly prevalent in patients with rheumatoid arthritis (RA). The prevalence of comorbidity in patients with RA is higher than in the Dutch general population (2-5). Estimates of the percentages of at least one comorbid condition vary substantially, ranging from 27%-81%, due to differences in the definition of comorbidity and selection of the study population (4-6). The average RA patient has approximately 1.6 comorbid conditions (7,8).

Comorbidities in patients with RA are both of a somatic and psychological nature. Common somatic comorbidities are cardiovascular disease, hypertension, chronic pulmonary disease, gastrointestinal disease, osteoporosis and infection (3,5,9,10). With regard to psychological comorbidity, depression is common and occurs in 13-20% of patients with RA. This is two to three times more common than in the general population (11-14).

There is increasing evidence that comorbidity plays an important role in determining RA-related outcomes. Evidence points to poorer outcomes after comorbidity in patients with RA than in the general population (2). Outcomes that are associated with comorbid conditions are disability, quality of life, health care costs and mortality (7,15). Both somatic comorbidity and comorbid depression are associated with negative outcomes, but different comorbid conditions have a different impact on health outcomes. For example, cardiac and pulmonary diseases are associated with greater rates of hospitalization and mortality, while depression is more strongly related to increased levels of disability (9).

Physical functioning, a major patient-reported outcome, is rated as the most important outcome in patients with RA. Rupp and colleagues (5) have shown that a somatic comorbid condition influences physical functioning negatively. Furthermore, they have also shown that depression is of major importance in predicting physical functioning (16). Radner and colleagues found that there was a negative influence of somatic comorbidity on all domains of physical functioning, independent of the level of disease activity (17,18). One study that investigated the influence of comorbidity on change in physical functioning demonstrated that comorbidity at baseline contributed negatively to change over time in physical functioning (19). They also found that nontreatment factors, such as age and comorbidity, had a greater effect on the progression in physical functioning than did treatment factors.

Most of the aforementioned studies investigated the influence of comorbidity over a 1-year period. Only one study used a 5-year followup period. However, little

is known about the impact of comorbidity in the longer term, which is important because it provides clinicians with long-term information about the possible course of physical functioning for individual patients. If the presence of comorbidity was found to influence physical functioning on a longer-term basis, it would be of even greater importance for clinicians to adjust their treatment to the comorbidity accordingly. Furthermore, the aforementioned studies that investigated the effects of comorbidity on physical functioning did not compare the influence of the co-occurrence of somatic comorbidity and comorbid depression. Comparing somatic comorbidity and comorbid depression is important because of their differential impact on patient-reported outcomes (20). Therefore, the aim of this study was to describe the long-term physical functioning in patients with RA and its association with somatic comorbidity and comorbid depression. Research questions consisted of: 1) How does long-term physical functioning develop in an RA population? 2) How are somatic comorbidity and comorbid depression associated with physical functioning? And 3) how are somatic comorbidity and comorbid depression associated with change in physical functioning?

PATIENTS AND METHODS

Study design and population

In 1997, a longitudinal study was started on comorbidity and health outcomes in patients with RA. At commencement, 1251 patients were randomly selected from an outpatient clinic for rheumatology and rehabilitation in Amsterdam or from an affiliated outpatient clinic. For inclusion in the study, patients had to fulfill the following eligibility criteria: a) having a diagnosis of RA according to the American College of Rheumatology Criteria for RA (21), being age ≥ 16 years, c) having adequate knowledge of the Dutch language, d) having had at least one visit to a rheumatologist in the previous 2 years.

Data were collected in 1997, 1998, 1999, 2002 and 2008 by means of self-administered questionnaires. The questionnaires comprised of questions about sociodemographic characteristics (age, sex, marital status, educational level and employment status), clinical characteristics (including comorbidity), health status (including physical functioning), and the utilization of health care services. Information on disease duration was retrieved from the patients' medical records.

In addition, we established whether participants had deceased during the period 1996-2010 from the mortality register of the Statistics Netherlands.

Measurements

Physical functioning

Physical functioning was measured with the validated Dutch version of the Health Assessment Questionnaire (HAQ) and, the physical functioning scales of the Dutch version of the RAND-36 (22). We used the physical functioning scales of the RAND-36 in addition to the HAQ to provide a more generic overview of physical functioning. With respect to the HAQ, the category score was raised when aids or devices were indicated by the patient. The RAND-36 is almost the same as the 36-item Short Form (SF-36) health survey (23). The physical component summary score (PCS) of the SF-36 was calculated according to the manual for SF-36 health summary scales (24) using Dutch population means, SDs, and factor score coefficients (25).

Comorbidity

Somatic comorbidity as well as comorbid depression were assessed at baseline. Somatic comorbidity was measured with a self-report list, adapted from the Health Interview Survey of the Statistics Netherlands (26). The Health Interview Survey covers 12 groups of chronic conditions, specifically lung diseases, cardiovascular diseases, diabetes mellitus, gastrointestinal diseases, cancer, kidney diseases, chronic infections, gall-bladder and liver diseases, chronic back complaints, skin diseases, thyroid gland diseases and neurological diseases. These chronic diseases are relatively most prevalent in The Netherlands. Respondents were asked to indicate whether they had had any of these conditions in the previous 12 months. Respondents indicating presence of one or more conditions were classified as having somatic comorbidity.

Comorbid depression was assessed with the Center for Epidemiological Studies Depression Scale (CES-D) (27). The CES-D is a short, self-administered scale designed to measure depressive symptomatology in the general population. The CES-D consists of 20 items and has a range of 0 to 60, with higher scores indicating more depressive symptoms. Scores ≥ 16 suggest presence of depression.

Control variables

The control variables included age, sex, socioeconomic status (SES), marital status and disease duration; these characteristics are prognostic factors regarding health outcomes (28-31). SES was indicated by educational level. We divided SES into 3 categories: low SES, indicating patients with no education or education at primary school level; medium SES, indicating patients with education at secondary school level; and high SES, indicating patients with a college or university level education. Marital status was dichotomised into married and single.

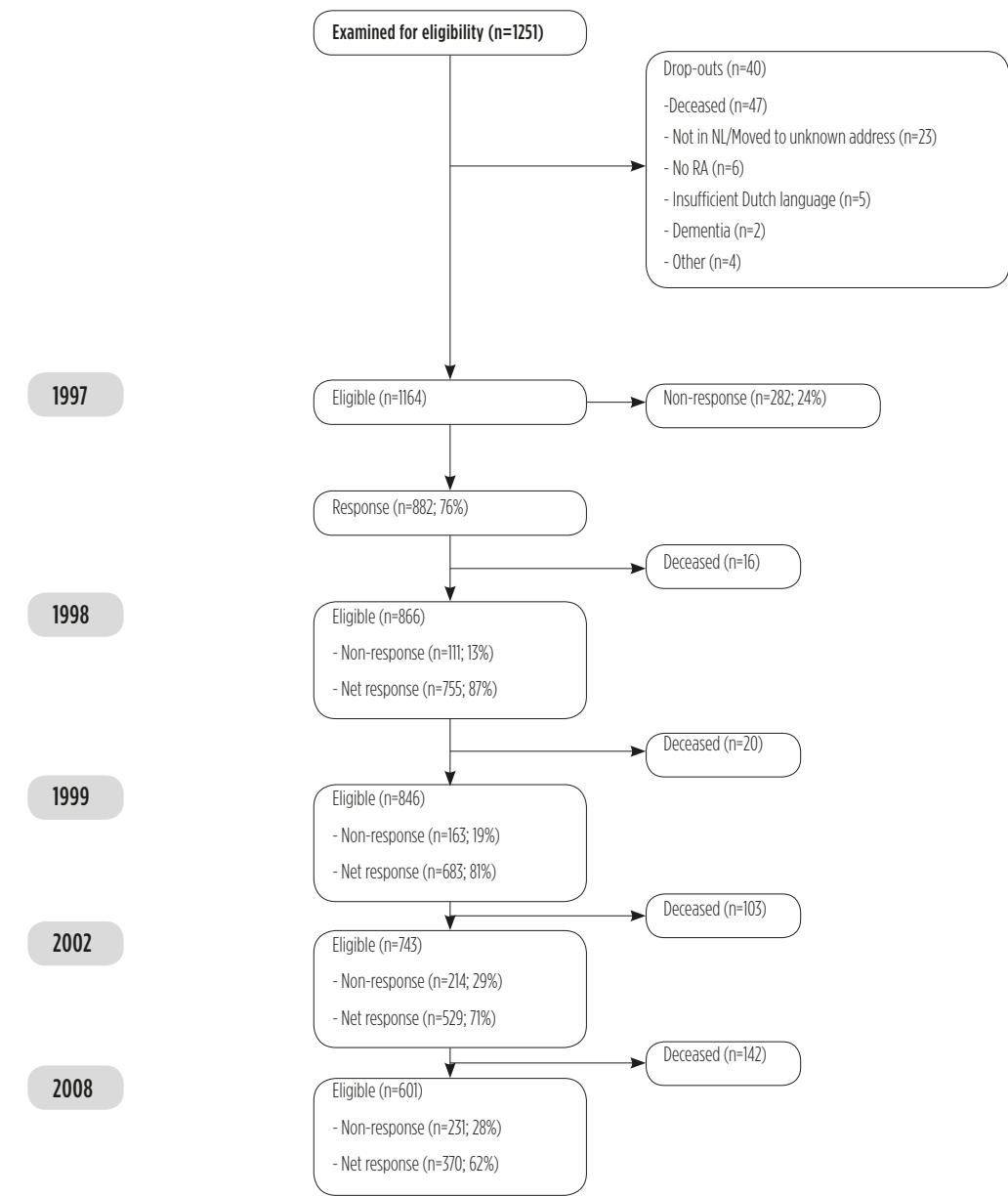


Figure 1. Flow chart of the rheumatoid arthritis (RA) cohort. Net response refers to the number of respondents in relation to the group of patients who responded in 1997 (n=882) and who were still alive at that measurement moment. Nonresponse is the number of patients who withdrew from the study plus patients who did not respond for one of the measurement moments. NL= The Netherlands.

Statistical analyses

To determine changes in physical functioning over time we performed a longitudinal analysis analyzing how baseline comorbidity predicts long-term physical functioning. Four groups based on the absence or presence of comorbidity at baseline were distinguished: 1) patients without comorbidity, 2) patients with somatic comorbidity only, 3) patients with comorbid depression only, and 4) patients with both somatic comorbidity and comorbid depression.

Analyses were carried out with the use of a linear, mixed-effect, random intercept model with serial correlation of the residuals (32). With this model, we controlled for intersubject correlation, taking into account that this correlation decreases with increasing time and for differences in duration between measurement moments. The outcome variable was physical functioning. The predictors were the comorbidity groups and their interaction with time. Time was entered as a continuous variable. We used 2 models: one model without and one model with the interaction between time and comorbidity groups. Separate analyses were performed for physical functioning measured with the HAQ and the SF-36. All models contained age, sex, SES, marital status and disease duration in order to control for possible confounding by these factors. All analyses were carried out using R, package lme4 (33). Results were considered statistically significant when *P* values were less than 0.05.

RESULTS

Response

A flow chart summarizing the followup process of the 1251 patients selected in 1997 is shown in Figure 1. Of the eligible patients, 882 (76%) returned the questionnaire in 1997. Of these patients, 755 (87% of the eligible patients) returned the questionnaire in 1998, 683 (81% of the eligible patients) in 1999, 529 (71% of the eligible patients) returned the questionnaire in 2002, and finally, 370 (62% of the eligible patients) returned the questionnaire in 2008.

Study population

Patient characteristics are summarized in Table 1. Patients with comorbidity were older, were more often women, and had a lower SES and a longer disease duration when compared with patients without comorbidity.

Long-term physical functioning for the total group

Table 2 provides the mean \pm SD scores on the HAQ and the SF-36 at baseline and followup for all respondents. The HAQ scores showed a small improvement in physical functioning between baseline and 11-year followup. The SF-36 scores also improved between baseline and 11-year followup (Table 2).

Long-term association between comorbidity and physical functioning

Table 2 and Figure 2 provide HAQ and SF-36 scores at baseline and followup for the comorbidity subgroups. Table 3 provides the results of the longitudinal analysis. Scores on the HAQ showed some difference in physical functioning between patients with somatic comorbidity and patients without comorbidity; however this difference was not statistically significant. On the other hand, outcomes of the SF-36 did show a significant difference between patients with somatic comorbidity and patients without comorbidity. Patients with comorbid depression demonstrated lower physical functioning than patients with somatic comorbidity and patients without comorbidity. In particular, the outcomes on the HAQ showed that there is a strong negative association of comorbid depression with physical functioning. Patients with both somatic and comorbid depression at baseline had the worst physical functioning.

Table 1. Description of study population at baseline

	Comorbidity						
	Total group (N=882)	None (n = 281)	Somatic (n= 328)	Depression (n=82)	Somatic & depression (n = 163)	Participants with complete follow-up (N=367)	Participants with incomplete follow-up (N =515)
Sex, N (%)							
Male	248 (28.1)	96 (34)	102 (31.1)	15 (18.3)	32 (19.6)	101 (27.5)	147 (28.5)
Female	634 (71.9)	185 (65.6)	226 (68.9)	67 (81.7)	131 (80.4)	266 (72.5)	368 (71.5)
Age, mean ± SD years	59.3 ± 14.8	56.7 ± 14.9	60.2 ± 13.9	59.2 ± 3.6	60.6 ± 15.2	53 ± 11.9	63 ± 15.3
Socioeconomic Status, N (%)							
Low	220 (24.9)	50 (17.8)	76 (23.2)	21 (25.6)	60 (36.8)	57 (15.5)	163 (31.7)
Middle	526 (59.6)	179 (63.7)	206 (62.8)	49 (59.8)	85 (52.1)	235 (64.0)	291 (56.5)
High	123 (13.9)	51 (18.1)	43 (13.1)	11 (13.4)	17 (10.4)	73 (19.9)	50 (9.7)
Missing	13 (1.5)	1 (0.4)	3 (0.9)	1 (1.2)	1 (0.6)	2 (0.5)	11 (2.1)
Marital Status, N (%)							
Single	315 (35.7)	84 (29.9)	111 (33.8)	38 (46.3)	70 (42.9)	92 (25.1)	223 (43.3)
Cohabitant	559 (63.4)	195 (69.4)	217 (66.2)	42 (51.2)	93 (57.1)	275 (74.9)	284 (55.1)
Missing	8 (0.9)	2 (0.7)		2 (2.4)			8 (1.6)
Disease duration median (IQR) years	5 (2-14)	5 (2-13)	5 (2-14)	4 (1-14)	7 (2-15)	6 (2-13)	4 (1-15)
DAS 28, mean ± SD	3.6 ± 1.3	3.4 ± 1.3	3.6 ± 1.3	3.8 ± .27	4.1 ± 1.39	3.5 ± 1.4	3.7 ± 1.35

Somatic comorbidity as indicated by score ≥ 1 on list of chronic diseases. Comorbid depression as indicated by score ≥ 16 on Center of Epidemiologic Depression Scale. IQR = Interquartile rang. DAS28 = Disease activity in 28 joints.

Long-term association between comorbidity and change in physical functioning

Table 2 and Figure 2 outline changes in the HAQ and SF-36 scores at baseline and followup for the comorbidity subgroups. Table 4 provides the results of the longitudinal analysis. Patients without comorbidity improved in physical functioning between baseline and 11-year followup. There was no difference in the change in physical functioning between patients with somatic comorbidity, patients with comorbid depression and patients without comorbidity, but there was a significant difference in the change in physical functioning between patients with both somatic and comorbid depression and patients without comorbidity. This indicates that the difference in physical functioning between both groups increased between baseline and 11-year followup.

Table 2. Physical functioning scores (mean ± SD) for the total study population and comorbidity subgroups

	1997 (n= 882)	1998 (n=755)	1999 (n=683)	2002 (n=529)	2008 (n=370)
HAQ					
Total group	1.14 ± 0.80	1.18 ± 0.81	1.22 ± 0.80	1.11 ± 0.75	1.11 ± 0.75
Comorbidity					
None	0.92 ± 0.73	0.94 ± 0.74	1.02 ± 0.76	0.95 ± 0.71	1.01 ± 0.73
Somatic	1.07 ± 0.77	1.15 ± 0.79	1.16 ± 0.76	1.02 ± 0.68	1.13 ± 0.73
Depression	1.49 ± 0.84	1.39 ± 0.84	1.47 ± 0.82	1.39 ± 0.74	1.32 ± 0.69
Somatic and depression	1.47 ± 0.79	1.55 ± 0.81	1.59 ± 0.79	1.51 ± 0.81	1.70 ± 0.81
SF-36 PCS					
Total group	36.1 ± 10.9	37.2 ± 11.1	36.4 ± 10.8	36.6 ± 11.0	39.0 ± 11.3
Comorbidity					
None	38.7 ± 10.4	40.4 ± 10.4	39.2 ± 10.8	38.4 ± 10.3	41.5 ± 10.4
Somatic	35.5 ± 11.1	36.4 ± 11.3	35.3 ± 10.8	36.7 ± 10.8	38.0 ± 10.9
Depression	33.5 ± 10.3	34.9 ± 10.2	34.0 ± 10.0	34.7 ± 11.0	38.3 ± 11.6
Somatic and depression	32.3 ± 10.1	33.1 ± 9.0	32.1 ± 9.7	32.0 ± 9.9	32.8 ± 10.3

HAQ = Health Assessment Questionnaire (range 0-3, were a lower score indicates better physical functioning); SF-36 = Short Form 36 (range 0-100, were a higher score indicates better physical functioning); PCS = physical component summary score.

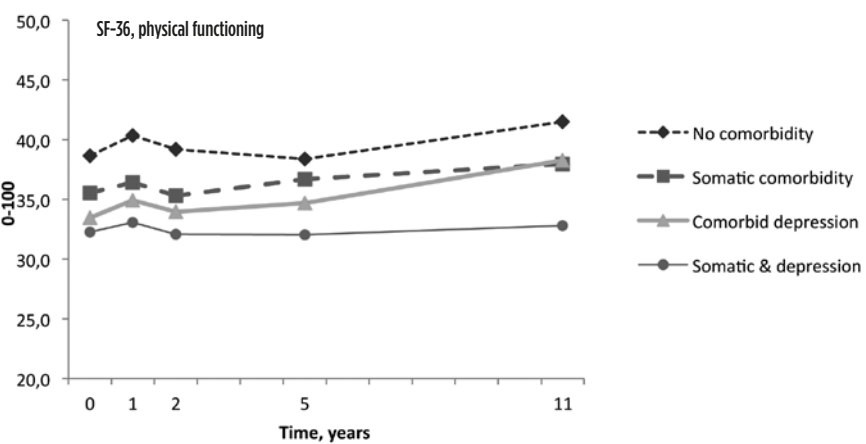
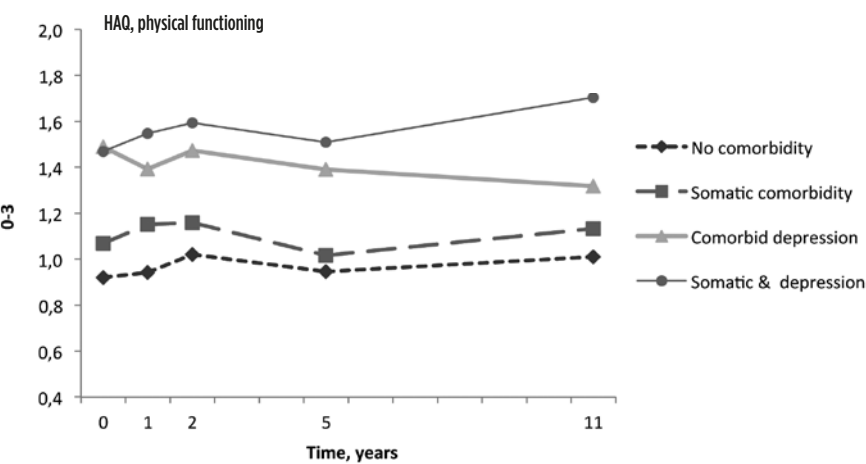


Figure 2. A, Physical functioning according to the Health Assessment Questionnaire (HAQ) over 11 years for the different comorbidity groups. A lower score indicates better physical functioning. **B,** Physical functioning according to the physical component summary score of the Short Form 36 over 11 years for the different comorbidity groups. A higher score indicates better physical functioning.

DISCUSSION

This study was conducted to determine the long-term change in physical functioning in patients with RA and the association with both somatic comorbidity and comorbid depression. Physical functioning improved slightly over 11 years for the total group. Somatic comorbidity and wcomorbid depression at baseline were negatively associated with physical functioning. This association remained over the entire 11-year period. RA patients with comorbid depression had the lowest level of physical functioning. Moreover, the combination of somatic comorbidity and comorbid depression was negatively associated with change in physical functioning over time.

Table 3. Differences in physical functioning between the reference group and patients with comorbidity at baseline over an 11-year followup period.

	HAQ				SF-36 PCS			
	Difference with reference group	p	95% CI		Difference with reference group	p	95% CI	
			lower	upper			lower	upper
Group without comorbidity (reference group)	0	-	-	-	0	-	-	-
Somatic comorbidity	0.09	0.10	-0.02	0.21	-2.80	< 0.01	-4.44	-1.18
Comorbid depression	0.45	< 0.01	0.27	0.62	-4.41	< 0.01	-6.69	-1.60
Somatic comorbidity and comorbid depression	0.44	< 0.01	0.31	0.58	-4.48	< 0.01	-6.85	-2.82

Estimates are from a longitudinal model, adjusted for age, sex, marital status, socioeconomic status, and disease duration, and assuming a constant difference between the comorbidity groups over time. HAQ = Health Assessment Questionnaire (lower score indicates better physical functioning); SF-36 = Short Form 36 (higher score indicates better physical functioning); PCS = physical component summary score; 95% CI = 95% confidence interval.

Table 4. Differences in change in physical functioning between patients with comorbidity and reference group at baseline over an 11-year followup period

	HAQ				SF-36 PCS			
	Annual change	p	95% CI		Annual change	p	95% CI	
			lower	upper			lower	upper
Group without comorbidity (reference group)	-0.02	< 0.01	-0.03	-0.01	0.52	< 0.01	0.353	0.679
Difference with reference group								
Somatic comorbidity	0.004	0.46	-0.007	0.016	-0.107	0.30	-0.031	0.093
Comorbid depression	-0.004	0.68	-0.026	0.016	-0.045	0.81	-0.397	0.324
Somatic comorbidity and comorbid depression	0.018	0.02	0.002	0.033	-0.369	0.01	-0.650	-0.083

Estimates are from a longitudinal model, adjusted for age, sex, marital status, socioeconomic status, and disease duration, with interaction between comorbidity group and time. HAQ = Health Assessment Questionnaire (lower score indicates better physical functioning). SF-36 = Short Form 36 (higher score indicates better physical functioning); PCS = physical component summary score; 95% CI = 95% confidence interval.

Our results showed an improvement in physical functioning between baseline and 11-year followup for the total group, on both the HAQ and the SF-36. Two other studies that investigated changes in physical functioning in patients with RA found a decline in physical functioning (19,34). These studies showed an annual increase in HAQ score of 0.01. In both studies, a substantial part of the progression in HAQ score was attributable to age, which was more visible in patients ages > 65-70 years. In our study, we controlled for age. Removing age from the model (data not shown) resulted in a smaller increase in physical functioning. Another explanation for the improvement in physical functioning could have been the introduction of new medication, which was introduced around 2001. Also, the process of response shift could explain the improvement in physical functioning. Response shift refers to the observation that many individuals tend to change the subjective evaluation of their health status as a result of changes in their objective health status (35). Finally, and although we took measures to reduce this possibility (see below), selection bias could have occurred.

From our results, we can conclude that baseline comorbidity was negatively associated with long-term physical functioning. Patients with somatic comorbidity, comorbid depression, or both comorbidities at baseline displayed worse physical functioning than patients without comorbidity. These findings are in line with studies that have investigated the impact of somatic comorbidity on physical functioning on the short term (17,18). Somatic comorbidity and comorbid depression are differentially associated with physical functioning. Comorbid depression resulted in lower physical functioning outcomes than somatic comorbidity. These results are in accordance with Baumeister et al, who emphasized the different impacts of somatic comorbidity and comorbid psychological disorders on quality of life, including physical functioning in patients with chronic, somatic diseases (20). Several studies support the association between depressive symptoms and poor physical functioning in patients with rheumatoid arthritis (13,36). Depression is linked to both the disease process and physical functioning by biological, behavioural, cognitive and social pathways (37). Authors of the studies on depression in RA state that clinicians should pay more attention to the RA patient's psychological well being (36). Our results further emphasise this, given the long-term impact of depression. Clinicians rarely examine psychosocial factors in clinical practice, and depression in patients with chronic somatic illnesses is often under diagnosed (38,39). Screening and treatment of comorbid depression would most likely contribute to improving clinical outcomes, particularly regarding physical functioning (36,40).

Only the combination of somatic comorbidity and comorbid depression was negatively associated with change in physical functioning over time, compared with the group of patients without comorbidity. Patients without comorbidity only slightly improve in physical functioning between baseline and 11-year followup. Patients with both somatic comorbidity and comorbid depression, however, did not improve in physical functioning. Michaud et al investigated which variables predicted change

in physical functioning over time, as measured with the HAQ (19). They found that comorbidity was an important predictor for change in physical functioning. In that study however, although both somatic comorbidity and comorbid depression were measured, the effects of having both types of comorbidity were not compared. Moreover, the mean followup period in their study was shorter (3.7 years).

The major strengths of our study are its longitudinal design, its long-term followup period, the large patient sample, and the relatively high response rate during the 11-year period. To our knowledge, this is the first study on the long-term association between comorbidity and physical functioning, as well as the differential association of somatic comorbidity and comorbid depression with physical functioning.

Loss to followup might introduce bias into longitudinal studies. In this study, we used a statistical model that took into account the selection bias that may have occurred. We optimized the estimation of physical functioning by adding all baseline demographic variables that are regarded as prognostic factors for health outcomes. The model assumes that nonresponders have the same physical functioning during followup as comparable responders, i.e., responders with equal values for all variables in the model. Therefore, the model fills in the data of nonresponders with data of comparable responders (responders that have the same physical functioning at baseline and are comparable in other variables used in this model). Although this reduces the risk of selection bias, there is still a risk of an incorrect estimation, e.g. if nonresponders have the same baseline scores as comparable responders, but the course of their physical functioning develops differently. Therefore, although this method is appropriate in addressing selection bias (41), it still remains a risk. In our study, information about physical functioning and comorbidity was collected with questionnaires. We did not have any information about use of medication. Because of this, we could not investigate the influence of new medications that were introduced between 2002 and 2008. However, we believe that all patients would have been treated according to the current insights at the time. Previous research has found that nontreatment factors have a greater effect on physical functioning than treatment factors (19).

In this study we only took into account the comorbid conditions that were present at baseline. It is possible that the improvement in long-term physical functioning was caused by a change in the number or severity of the comorbid conditions. Although it is possible that some comorbidities that were present at baseline disappeared or became less severe at followup, it seems more likely that during followup patients developed more or more severe comorbidities (42). Therefore, a change in the number or severity of comorbidities does not seem to be a likely explanation for the improvement in long-term physical functioning.

Finally, comorbidity was measured as a dichotomous variable. Levels of severity were not measured. Stronger associations might have been found if the levels of severity had been assessed.

Our results stress the importance of paying attention to comorbid conditions in clinical practice. They show that patients without comorbidity report stable, or even a slight improvement in, physical functioning over time. Patients with comorbidity, and in particular patients with both somatic comorbidity and comorbid depression, however remain behind in physical functioning over 11 years of followup. For the HAQ, the difference in change in physical functioning score for the group of patients with both somatic comorbidity and comorbid depression compared with the group without comorbidity was 0.018 annually. When multiplying this difference by 11 years, the difference in change between both groups after 11 years is clinically significant (43). This means that if a patient with RA has both somatic comorbidity and comorbid depression at a particular time point, there is an increased risk that he or she shows clinically significantly worse outcomes in physical functioning after 11 years. As such, it is important to ascertain the presence of such comorbidities at an early stage so treatment can be adjusted. Integrating a routine screening process for both somatic and comorbid depression in patients with RA is recommended. In addition, intervention strategies should be developed for the adequate treatment and management of somatic and psychological comorbidities, to reduce their negative impact on physical functioning and to improve clinical outcomes. This requires integration of care of different professions. Alongside pharmacological treatment aimed at improving disease activity, multidisciplinary rehabilitation can further improve physical functioning by booking improvements in functional ability and psychological and social health via nonpharmacological treatment modalities (44).

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Chapter 3

Physical and mental functioning
in patients with established
rheumatoid arthritis over
an 11-year followup period:
the role of specific comorbidities

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followup period: the role of specific comorbidities. *The Journal of
Rheumatology* 2016; 43: 307-14.

ABSTRACT

Objective. To investigate the longterm association of a wide range of comorbidities with physical and mental functioning in patients with rheumatoid arthritis (RA).

Methods. Longitudinal data over a period of 11 years were collected from 882 patients with RA. Somatic comorbidity and comorbid depression were measured at baseline, with a questionnaire including 20 chronic diseases and with the Center for Epidemiologic Depression Scale, respectively. Physical functioning was measured at 5 timepoints with a disease-specific measure [Health Assessment Questionnaire (HAQ)] and a generic measure [physical scales of the Medical Outcomes Study Short Form-36 (SF-36)]. Mental functioning was measured with the mental scales of the SF-36. To determine the association of baseline specific comorbidities with functioning over time we performed longitudinal analyses.

Results. At baseline, 72% percent of the patients was female, mean age \pm SD was 59.3 ± 14.8 years, median RA disease duration was 5.0 years, and 68 % had ≥ 1 comorbid condition. The effect of comorbid conditions was more apparent when physical functioning was measured with SF-36, a disease-generic measure, compared with the HAQ, a disease-specific measure. Circulatory conditions and depression were associated ($p < 0.05$) with worse physical functioning according to the HAQ. Respiratory conditions, musculoskeletal conditions, cancer and depression were associated ($p < 0.05$) with worse physical functioning according to the SF-36. Respiratory conditions and depression were associated with worse mental functioning.

Conclusion. Patients with specific comorbid conditions have an increased risk of low functioning in the long term. Targeted attention for these specific comorbid conditions by clinicians is recommended.

INTRODUCTION

Comorbidity, defined as any additional, coexistent condition in a patient with a particular index disease (1), is highly prevalent (2) in patients with Rheumatoid Arthritis (RA) and is involved in determining RA-related outcomes (3). Several studies have reported the negative association of somatic comorbidity with physical functioning (3-5). Somatic comorbidity is, even after 10 years, associated with worse physical functioning and contributes over time to decline in physical functioning (2,3,6). The effect of somatic comorbidity on mental functioning is less well known. Comorbid depression is associated with low physical functioning (6,7) and mental functioning (8,9).

In most studies, comorbidity is measured with a dichotomous (6) score, a sum score (3), or an index score (10,11). In clinical practice a clinician needs to determine the prognosis of individual patients with specific comorbidities. Evaluating specific comorbidities provides valuable prognostic information for clinical practice about which patients have a higher risk for worse functioning in the long term, and treatments could be adjusted accordingly. Therefore, knowledge is required of the effect of baseline comorbidity on functioning (12).

The effects of specific comorbidities on physical and mental functioning will be different. It may be expected that different chronic diseases show varying effects on physical functioning, but do not differ much in their effect on mental functioning because the adaptation process of chronic diseases is comparable (13). Few studies have investigated the effect of a specific comorbid condition on physical functioning (14,15). To our knowledge, the effect of specific comorbidities on mental functioning has not yet been investigated. Chronic diseases often have a course of slow decline and therefore it is expected that the impact of comorbidity will be more clear on the longer term. A longtime horizon is needed to investigate which specific comorbidities are associated with worse physical and mental functioning over time.

Therefore, the aim of our study was to investigate the association of a wide range of comorbidities with physical and mental functioning during 11 years of followup in patients with RA. Research questions consisted of 1) which specific comorbidities are associated with low physical functioning, and 2) which specific comorbidities are associated with low mental functioning. More insights into the effect of comorbidity will contribute to optimizing the medical management of patients with RA.

PATIENTS AND METHODS

Study design and population

In 1997, our research group started a longitudinal study on comorbidity and health outcomes in patients with RA (16). A sample of 1251 patients was randomly selected from the register of a large rheumatology outpatient clinic in Amsterdam, which included the patients from 7 allied outpatient clinics. For inclusion in the study, patients had to fulfill the following eligibility criteria: 1) a diagnosis of RA according to the American College of Rheumatology criteria for RA, 2) 16 years of age or older, 3) adequate knowledge of the Dutch language, and 4) at least 1 visit to a rheumatologist in the previous 2 years.

Data were collected in 1997, 1998, 1999, 2002 and 2008 by means of self-administered questionnaires. The questionnaires consisted of questions about sociodemographic characteristics (age, sex, educational level, and employment status), clinical characteristics (including comorbidity) and health characteristics (including physical and mental functioning). Information on RA disease duration was retrieved from the patients' medical records, and disease activity was assessed during clinical examination. In addition, we established whether participants had deceased during the period 1996-2011 from the mortality register of the Statistics Netherlands (17).

Measurements

Demographic and clinical variables

The sociodemographic variables included age, sex and socioeconomic status (SES). SES was indicated by educational level. We divided SES into 3 categories: low SES (no education or education at the primary school level), medium SES (education at the secondary school level), and high SES (college or university level education).

Disease activity was assessed by means of the Disease Activity Score (DAS) in 28 joints, scoring separately swelling and tenderness of 28 joints (and without using the visual analogue scale for general health assessment).

Physical and mental functioning

Physical functioning was measured with the validated Dutch version of the Health Assessment Questionnaire (HAQ), a disease-specific measure of physical functioning. The HAQ category score was raised when aids or devices were indicated by the patient. In addition, physical functioning was measured with the physical functioning scales of the Dutch version of the RAND-36 (18). This is a generic measure of physical functioning, meaning that its concepts are not specific to any disease or treatment group (19). Mental functioning was measured with the mental scales of the Dutch version of the RAND-36. Given the reported minimal differences between the RAND-36 and the Medical

Outcomes Study Short Form-36 (SF-36), a physical component summary (PCS) and a mental component summary (MCS) were calculated according to the manual for SF-36 health summary scales using Dutch population means, SD, and factor score coefficients (20). The summary scores are normally distributed with a mean of 50 and a standard deviation of 10 (21).

Comorbidity

Comorbidity was assessed at baseline. Somatic comorbidity was measured with a list adapted from the Health Interview Survey of the Statistics Netherlands (22), a validated list amenable to self-reporting (23). This list covers 20 chronic conditions that are prevalent in the Netherlands; most of them are also prevalent in RA (12,24). Respondents were asked to indicate whether they had had any of the conditions in the previous 12 months. The following 9 categories of chronic somatic comorbidity were created based on the body systems involved: (1) circulatory conditions (myocardial infarction or other serious heart disorders, stroke), (2) respiratory conditions (asthma or chronic bronchitis), (3) digestive conditions (disorders of the stomach, disorders of the liver, disorders of the gall bladder, serious disorder of the intestine longer than 3 months), (4) genitourinary conditions (disorders of the kidneys, kidney stones, inflammation of the bladder), (5) neurological conditions (migraine, dizziness with falling, epilepsy), (6) musculoskeletal conditions (hernia or chronic back complaints), (7) endocrine, metabolic and nutritional conditions (diabetes mellitus, disorders of the thyroid gland), (8) cancer, and, (9) a rest category (hypertension, infection of the nasal cavity or frontal sinus, skin conditions). These 9 categories are in accordance with previous research also using the list about somatic comorbidity from the Health Interview Survey of the Statistics Netherlands (25).

Comorbid depression was assessed with the Centre for Epidemiological Studies-Depression Scale (CESD) (26). The CESD is a short self-administered scale designed to measure depressive symptomatology in the general population. The CESD consists of 20 items and has a range of 0 to 60, with higher scores indicating more depressive symptomatology. Scores of ≥ 16 suggest presence of depression.

Statistical analyses

To determine the impact of specific comorbid conditions on functioning over time we performed a longitudinal analysis, analysing how baseline comorbidity predicts longterm physical and mental functioning. Analyses were carried out with the use of a linear random intercept (mixed-effect) model with serial correlation of the residuals (27). With this model, we controlled for inter-subject correlation, taking into account that this correlation decreases with increasing time, and for differences in duration between measurement moments. A model was used with time and all categories of comorbidity as independent variables and the outcome at baseline, 1-, 2-, 5- and 11-years

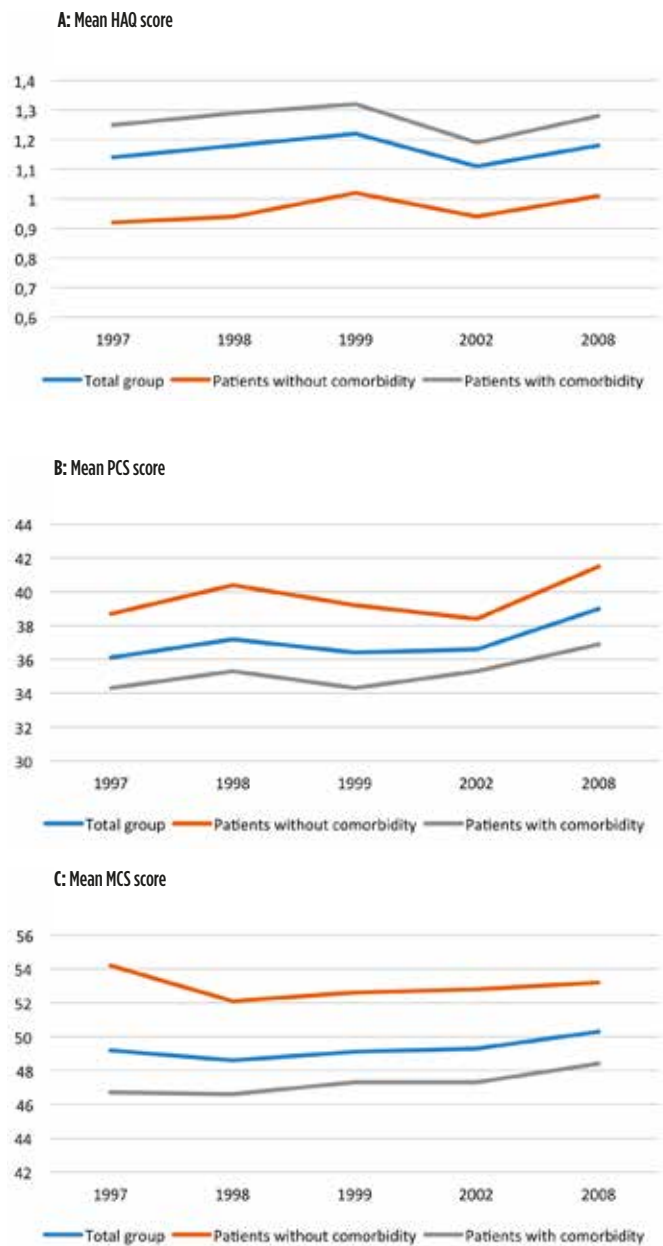


Figure 1. A. Physical functioning according to the HAQ over 11 years for the total group of patients, patients without baseline comorbidity and patients with baseline comorbidity. A lower HAQ score indicates better physical functioning. **B.** Physical functioning according to the PCS of the SF-36 over 11 years for the total group of patients, patients without baseline comorbidity and patients with baseline comorbidity. A higher PCS score indicates better physical functioning. **C.** Mental functioning according to the MCS of the SF-36 over 11 years for the total group of patients, patients without baseline comorbidity and patients with baseline comorbidity. A higher MCS score indicates better mental functioning. HAQ = Health Assessment Questionnaire, PCS = physical component summary, SF-36 = Medical Outcomes Study Short Form-36, MCS = mental component summary.

followup as dependent variables. The predictors were the categories of comorbidity. Time was entered as a continuous variable. Separate analyses were performed for the outcome physical functioning, measured with a disease-specific measure (HAQ) and with a generic measure (SF-36), and for mental functioning.

Loss to follow-up might introduce bias into longitudinal studies. In our study, we used a statistical model that took into account the selection bias that may have occurred. The model assumes that nonresponders have the same physical and mental functioning during followup as comparable responders; that is, responders with equal values for all variables in the model. Therefore, the model fills in the data of nonresponders with data of comparable responders (those who have the same physical functioning at baseline and are comparable in other variables used in this model).

All models contained age, sex, RA disease duration and DAS score to control for possible confounding by these factors. To enhance the interpretability of the regression coefficients, we subtracted mean age from the variable age, median RA disease duration from the variable RA disease duration and mean DAS score from the variable DAS score. All analyses were carried out using R, package lme4 (28). Results were considered statistically significant when p values were <0.05.

RESULTS

Response

Of the eligible patients, 882 (75%) returned the questionnaire in 1997. Of these patients, 755 (crude response 85%; net response, the response in patients still alive, was 87%) returned the questionnaire in 1998, 683 (crude response 77%; net response 81%) in 1999, 529 (crude response 60%; net response 71%); in 2002, and finally, 370 (crude response 42%; net response 62%) returned the questionnaire in 2008. During the study period, 285 patients died (6).

Study population

Patient characteristics are shown in Table 1. Of all RA patients at baseline, 72% was female, the mean age was 59.3 (SD 14.8) years and the median RA disease duration was 5.0 (IQR 2.0-14.0) years. At baseline, 67.9% had ≥ 1 comorbid condition. Comorbid conditions that were most common were as expected conditions in the rest category (hypertension, conditions of the nasal cavity and frontal sinus and skin conditions), depression and musculoskeletal conditions.

Longterm association between comorbidities and physical and mental functioning

Figure 1 presents the trajectories of physical and mental functioning for the total group of patients, patients without comorbidity and patients with comorbidity. In addition,

table 2 provides the mean physical and mental functioning scores over an 11-year period, and the difference in physical and mental functioning between patients with RA with a specific comorbid condition and patients with RA without comorbidity. The mean HAQ score for an average patient with RA without comorbidity was 0.99. The same patient with a comorbid circulatory condition at baseline had a mean HAQ score of $0.99 + 0.23 = 1.22$. Results showed higher HAQ scores and thus worse physical functioning in RA patients with circulatory conditions and depression.

Scores on the SF-36 showed lower scores and thus worse physical functioning in patients with RA with respiratory conditions, musculoskeletal conditions, cancer and depression. For example, an average patient without comorbidity had a mean PCS of 37.85. The same patient with a comorbid respiratory condition and with comorbid depression had a mean PCS of $37.85 - 2.12 - 2.76 = 32.97$.

Table 1. Description of rheumatoid arthritis study population at baseline (n=882)

Sex, N (%)		
Male	248	(28.1)
Female	634	(71.9)
Age, mean ± SD	59.3	± 14.8
RA disease duration in yrs, median (IQR)	5.0	(2.0-14.0)
DAS 28, mean ± SD	3.6	± 1.3
Socioeconomic status, N (%)		
Low	220	(24.9)
Middle	526	(59.6)
High	123	(13.9)
Missing	13	(1.5)
Comorbidity, N (%)		
None	283	(32.1)
Circulatory conditions	49	(5.6)
Respiratory conditions	117	(13.3)
Digestive conditions	84	(9.5)
Genitourinary conditions	43	(4.9)
Neurologic conditions	91	(10.3)
Musculoskeletal conditions	121	(13.7)
Endocrine, metabolic and nutritional conditions	82	(9.3)
Cancer	18	(2.0)
Rest category	274	(31.1)
Depression	251	(28.5)

IQR = Interquartile range, SD = Standard deviation, DAS = Disease Activity Score in 28 joints.

Patients with RA with respiratory conditions and depression presented lower scores and thus worse mental functioning. For example, a patient without comorbidity had a mean MCS score of 53.03. A patient with a comorbid respiratory condition had a mean MCS of $53.02 - 2.21 = 50.82$.

DISCUSSION

Our study provides information about which specific comorbid conditions are associated with worse longterm physical and mental functioning in patients with RA. Knowledge about the effect of specific comorbidities provides clinicians information about target groups who are at risk for worse longterm functioning, facilitating early referral and treatment of these specific groups.

Table 2: Differences in physical and mental functioning between patients with rheumatoid arthritis with specific comorbidities and patients with rheumatoid arthritis without comorbidity. Adjusted for age, sex, disease duration, disease activity, and all other comorbidities

Table 2a. Physical functioning HAQ				
Patients with RA without comorbidity	Mean HAQ score over 11 years			
	0.99			
	Difference in HAQ score		95% conf interval	
	when comorbidity	p	lower	upper
Circulatory conditions	0.23	0.02	0.03	0.43
Respiratory conditions	0.02	0.81	-0.12	0.16
Digestive conditions	0.06	0.45	-0.10	0.22
Genitourinary conditions	0.02	0.84	-0.31	0.26
Neurological conditions	0.12	0.15	-0.04	0.28
Musculoskeletal conditions	0.09	0.20	-0.05	0.22
Endocrine, metabolic and nutritional conditions	0.06	0.46	-0.10	0.22
Cancer	0.22	0.18	-0.10	0.54
Rest category	0.01	0.84	-0.09	0.11
Depression	0.34	0.00	0.24	0.44
Age	0.01	0.00	0.00	0.01
Sex	-0.27	0.00	-0.38	-0.17
Disease duration	0.01	0.00	0.01	0.02
Disease activity	0.20	0.00	0.16	0.25

range: 0-3 higher score indicates worse physical functioning

At the beginning of the study, 75% of the patients returned the questionnaire. Rupp, *et al* investigated in a previous study for this cohort whether respondents differed at baseline from nonrespondents (29). For this purpose, nonrespondents were approached by telephone interview. Results showed that respondents were in general comparable to nonrespondents. Nonrespondents did have less pain and used specific health-care services less often.

To study the effect of somatic comorbidities on functioning, we used a list that covers the chronic conditions that are most prevalent in the general population in the Netherlands. Most of these comorbidities are also prevalent in patients with RA (12,14,24). The effect of 2 comorbidities, osteoporosis and infection, which are specifically highly prevalent in patients with RA (24,30), but not specified in the National Health Interview Survey, could not be addressed in this study. Future research should also specifically address the impact of osteoporosis and infection on functioning.

We used a statistical model that assumes that the outcomes of nonresponders (dropouts) are equal to the outcomes of responders who are comparable in baseline characteristics. This statistical method minimizes the risk of selection bias in case of difference between nonresponders and responders (31). Although this model reduces the risk of selection bias, this type of bias cannot completely be ruled out.

Comorbid circulatory, respiratory, musculoskeletal conditions, cancer and depression impaired the longterm physical functioning of patients with RA independent of age, disease duration and disease activity. The HAQ is often used in RA to survey the severity of the disease. Pope, *et al* found that a HAQ score of -0.21 corresponded to a minimally important difference (32). If we apply these results to our study, circulatory conditions and depression showed not only a statistically significant but also a clinically significantly worse score on the HAQ (32, 33). Scores of the SF-36 physical functioning showed that patients with RA without comorbid conditions still had a much lower

Table 2b. Physical functioning | SF-36

	Mean PCS score over 11 years			
	37.85			
	Difference in PCS score		95% conf interval	
	when comorbidity	p	lower	upper
Circulatory conditions	-2.56	0.07	-5.34	0.21
Respiratory conditions	-2.12	0.03	-4.07	-0.18
Digestive conditions	-1.18	0.30	-3.42	1.06
Genitourinary conditions	-1.74	0.30	-5.02	1.55
Neurological conditions	-1.49	0.19	-3.71	0.73
Musculoskeletal conditions	-2.63	0.01	-4.50	-0.75
Endocrine, metabolic and nutritional conditions	-2.02	0.08	-4.28	0.25
Cancer	-4.59	0.05	-9.12	-0.06
Rest category	0.16	0.83	-1.26	1.58
Depression	-2.76	0.00	-4.22	-1.30
Age	-0.05	0.03	-0.10	-0.01
Sex	2.27	0.00	0.82	3.73
Disease duration	-0.15	0.00	-0.21	-0.09
Disease activity	-2.97	0.00	-3.54	-2.39

range 0-100 lower score indicates worse physical functioning

Table 2c. Mental functioning | SF-36

	Mean MCS score over 11 years			
	53.02			
	Difference in mean		95% conf interval	
	when comorbidity	p	lower	upper
Circulatory conditions	-1.36	0.30	-3.92	1.21
Respiratory conditions	-2.21	0.02	-4.02	-0.41
Digestive conditions	-1.00	0.34	-3.07	1.06
Genitourinary conditions	-0.82	0.59	-3.83	2.20
Neurological conditions	-0.85	0.41	-2.90	1.19
Musculoskeletal conditions	-0.49	0.58	-2.22	1.24
Endocrine, metabolic and nutritional conditions	0.81	0.45	-1.29	2.90
Cancer	0.72	0.74	-3.50	4.94
Rest category	-0.31	0.64	-1.62	1.00
Depression	-12.75	0.00	-14.10	-11.40
Age	-0.04	0.09	-0.08	0.01
Sex	0.57	0.41	-0.77	1.91
Disease duration	0.04	0.19	-0.02	0.10
Disease activity	-0.31	0.25	-0.84	0.22

range 0-100 lower score indicates worse mental functioning

RA = rheumatoid arthritis, HAQ = health assessment questionnaire, SF-36 = Medical Outcomes Study Short Form-36, PCS = physical component summary, MCS = mental component summary

physical functioning than the mean score of 50 for in the people in the general population (21). When patients with RA also had a respiratory or musculoskeletal condition, cancer or depression, their physical functioning was even worse. Kosinski, *et al* found that a PCS score of 3.1 indicates a minimally important change (34). If we apply these result to our study, patients with cancer showed not only statistically significant but also a clinically significantly worse physical functioning (33).

Depression was associated with clinically significantly worse physical functioning, measured with both the HAQ and the SF-36. This corresponds to other studies. Moussavi, *et al* found that the combination of depression and arthritis was cross-sectionally associated with lower health status, more than depression alone, arthritis alone or 2 somatic conditions (35). Morris, *et al* found depression and even intermittent depression over time was associated with low self-reported health status and disability after 18 years (36). Depression is linked to RA and physical functioning by biological, behavioural, cognitive and social pathways (37-40). Psychological interventions have been shown to have a favourable effect on physical functioning in patients with RA (41,42).

The baseline prevalence of depression was, in comparison with the somatic comorbidities, relatively high (28.5%). It is difficult to compare the prevalences of comorbid depression and the somatic comorbidities, because these prevalences were estimated using different measures. The high prevalence of depression is, however, in accordance with the literature (24).

To provide both disease-specific and a generic overview of physical functioning, we used both the HAQ and the physical scales of the SF-36. The HAQ is disease-specific; it asks for specific activities which are often related to RA, while the SF-36 is a generic measure, meaning that functioning is assessed in a general way - not specific to any age, disease or treatment group (19). Our results showed that the impact of comorbid conditions is more apparent when physical functioning is measured with the SF-36. Given the high prevalence of comorbidity in patients with RA (in this cohort, more than two-thirds of the patients had ≥ 1 comorbid condition at baseline), we recommend adding the SF-36 to the HAQ to capture a full spectrum of functioning.

Respiratory conditions and depression were associated with worse mental functioning. To our knowledge, ours is the first study in patients with RA that investigated the association between specific comorbidities and mental functioning. A study that compared mental functioning among patients with different chronic diseases also showed that patients with respiratory conditions had the lowest mental functioning (43). This could be because of the loss of independence, low control over disease and physical disability. In addition, it seems that in respiratory diseases, because of the limited exercise tolerance and dyspnoea anxiety is involved (44).

Considerations

The strengths of our study were its longitudinal design and its longterm followup period. Moreover, a wide spectrum of somatic comorbid conditions and comorbid depression was investigated, and both physical and mental functioning were investigated.

In our study, the goal was to investigate the effect of a specific comorbid condition on the longterm functioning. We did not investigate the association of combinations of comorbidities with functioning, although it is likely that many patients had > 1 comorbid condition. However, scores of patients having > 1 comorbid condition can be calculated from the data in Table 2.

The associations between specific comorbidities and functioning might differ for patients depending on age, sex, or the presence of other comorbidities. Therefore, additional analyses were performed. No significant interactions were found between comorbidities with significant main effects and age, between these comorbidities and sex, and among these comorbidities (data not shown). This indicates that the associations between specific comorbidities and functioning do not depend on age, sex, or the presence of other comorbidities. Treatment strategies as well as the classification of RA changed in the years our study was conducted. As a consequence, it is possible that the effect of the specific comorbidities on functioning changed over time. The short-term effect of baseline predictors on functioning could differ from the longterm effect. We tested this assumption by 2 additional linear regression analyses, in which we studied the effect of baseline predictors on functioning in 1998 and in 2008. The results of these 2 linear regression analyses were similar to the results of the longitudinal analyses (data not shown). This indicates that the effect of the baseline predictors on functioning is stable over time.

Clinical relevance

Our RA study demonstrates that comorbid circulatory conditions, respiratory conditions, musculoskeletal conditions, cancer and depression were associated with low physical functioning, while respiratory conditions and depression were associated with low mental functioning. Patients with these comorbidities had an increased risk of worse functioning on the long term. Moreover, physical functioning was also clinically significantly worse for patients with circulatory conditions, cancer and depression and mental functioning was clinically significantly worse for patients with depression.

A recent study showed that the detection and management of comorbidities in RA is far from optimal (24). We recommend that clinicians assess comorbidity systematically in medical management because of the longterm effect of comorbidity on functioning. Raising the awareness of comorbidity in patients with RA could contribute to increasing the quality of care for these patients.

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Chapter 4

Mortality in patients with rheumatoid arthritis: a 15-year prospective cohort study

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Rheumatology International 2017; 37: 487-493.

ABSTRACT

Objectives. The aim of this study was to investigate a) the mortality in a clinical cohort of patients with established rheumatoid arthritis (RA) in comparison with the general Dutch population over 15 years, b) the trend in the mortality ratio during the study period, and c) causes of death and compare these with the general population.

Methods. In 1997, a sample of 1222 patients was randomly selected from the register of a large rheumatology outpatient clinic. Their mortality and primary causes of death between 1997 and 2012 were obtained from Statistics Netherlands. The Standardized Mortality Ratio (SMR) for all-cause mortality and the number of life-years lost in the study period, adjusted for age, sex, and calendar year, were calculated. A linear Poisson regression analysis was performed to evaluate change in all-cause SMR over time. Finally, the SMRs for cause-specific mortality were calculated.

Results. The mean age of the population at baseline was 60.4 (*SD* 15.4) years and 72.6% of the patients were women. The estimated SMR (95% CI) for all-cause mortality was 1.54 (1.41, 1.67) with about one life-year lost over the study period. There was a trend to decreasing SMR (2% annually, $p = .07$). Mortality was higher compared with the general population for circulatory system diseases, respiratory system diseases, musculoskeletal system diseases, and digestive system diseases ($p < .05$).

Conclusion. The observed mortality among patients with RA was 54% higher than in the general population after adjustment for age, sex and calendar year. More than one life-year was lost over 15 years, and the mortality tended to decrease over time. The mortality was higher for cardiovascular, respiratory, musculoskeletal and digestive diseases.

INTRODUCTION

Patients with rheumatoid arthritis (RA) have a higher mortality risk than the general population. Mortality rates in persons with RA are around 1.5 times higher than in the general population, with similar patterns over the last 50 years (1).

Causes of death that are increased in comparison with the general population are cardiovascular (CV) diseases, respiratory diseases and infections. The higher mortality rate is particularly caused by CV disease (2-7), but only partly caused by the higher prevalence of CV risk factors (8,9). The additional risk depends on systemic inflammation (10). Other increased causes of death are respiratory diseases and infections (6,7,11) most often due to respiratory infection/pneumonia (4-6). The increased infection risk may be attributed to the impaired immune function in RA or an effect of immunosuppressive therapy. In the most recent studies investigating cause-specific mortality, only a limited number of causes of death were studied (12), the number of patients who died during follow-up was small, and most data came from studies conducted before 2004 (11,13). There is thus a need to study the cause-specific mortality for a wide range of causes, in a large cohort, using more recent mortality data.

The treatment of patients with RA has been improved over time. The focus is now on tight disease control with much earlier initiation of intensive treatment (14). From the 1990s, high-dose treatment with disease-modifying anti-rheumatic drugs (DMARDs), particularly methotrexate started and biologicals were applied from 2000 onwards. Meta-analyses suggest that DMARDs (particularly methotrexate) reduce CV risk (15) and there is accumulating observational evidence that this also applies for biologicals, particularly the TNF-blockers (16,17).

Although the management of RA has improved, outcomes about mortality rates of observational studies that started around 2000 differ. Some studies report that the mortality in patients with RA was similar to that of the general population (18,19), while other studies showed that the mortality in patients with RA was higher (20,21) or that the mortality gap with the general population was even increasing (11). Reason for the different results can be the changing RA treatment during the last two decades as described above (14) or to the different types of cohorts and followup time (22). Given these conflicting results, there is thus also an obvious need to evaluate the risk of mortality in a large sample of patients with RA, over a long period, using more recent mortality data. The need to study the mortality in long-term clinical cohorts of RA patients was underscored by a recent editorial (23).

Hence, the objectives of this study were a) to investigate the mortality in a clinical cohort of patients with established RA and to compare this with the general Dutch

population, b) to assess the trend in the mortality ratio during the study period, and c) to examine the causes of death.

PATIENTS AND METHODS

Study design and population

In 1997, our research group started a cohort study on comorbidity (24) and the impact on health outcomes and mortality (25-27) in patients with RA. A sample of 1222 patients was randomly selected from the register of a large rheumatology outpatient clinic in Amsterdam, which included the patients from seven allied outpatient clinics. For inclusion in the study, patients had to fulfil the following eligibility criteria: a) be diagnosed with RA according to the American College of Rheumatology (ACR) Criteria for RA (28), b) be 16 years of age or older, and c) have visited a rheumatologist at least once in the previous 2 years.

Assessments

All 1222 patients were linked to Statistics Netherlands' mortality records for the period 1997-2012 (29,30). The linkage of the patients to the mortality data was anonymous, using only date of birth, sex, and, if available, civil registration number, and was performed by staff of Statistics Netherlands (31). Its databank provides death/life status, death dates, and primary and secondary causes of death. For this study, we used primary causes of death only. Causes of death were classified according to the Internal Classification of Diseases system (ICD-10) of the World Health Organization (32). For patients who could not be linked to these records, data were obtained from the outpatient clinic register. In order to compare patients with the general population, age and sex specific mortality data and causes of death for the general population were provided by Statistics Netherlands (30).

Statistical analyses

The standardized mortality ratio (SMR) was computed in order to compare the mortality in the RA cohort with the general population. The SMR was calculated as the ratio of the number of observed deaths in a study population divided by the number of expected deaths if the study population had the same age, sex, and calendar year specific rates as the general population. To calculate the expected death rates, we used the mortality rates of all Dutch inhabitants. So, in calculating the expected number of deaths there was adjusted for age, sex, and calendar year. We calculated the SMR for all-cause mortality, for each year, the mean of 3 years, the mean of 5 years, and the mean of all 15 years.

The number of life-years lost was calculated as follows. First, the partial life expectancy for the RA cohort was calculated from the start of the study to 15 years later.

This was also done for the general Dutch population, using a sex and age matched cohort. Second, we calculated the difference in the expected life-years during the study period between the RA cohort and the general population.

To investigate if there was a trend towards an increase or decrease in the SMR over time a Poisson regression analysis was performed with log link function. Because there are only a few points in time a simple model was used. Both identity link function and log link function showed a good fit when checking the deviance of the residuals (33).

Because the exact date of inclusion in the cohort was not clear, and as this might bias the calculated SMR for this year, the 1997 data were excluded from this analysis.

Finally, the SMR for cause-specific mortality was calculated. Because of limited numbers, we calculated the mean SMR for all 15 years.

RESULTS

Study population

Of the 1222 patients who were selected at baseline, 1208 patients (99%) could be linked to Statistics Netherlands. Of the 14 patients who could not be linked, 5 died, according to the outpatient clinic's register. For these 5 patients no information about cause-specific mortality was available. No information about mortality could be obtained for 9 patients. These 9 patients were excluded from the analyses. Therefore, data of 1213 patients were used for our analyses. The mean age of these patients at baseline was 60.4 (SD 15.4) years and 72.6% of the patients were women. Data on disease duration were available for a subcohort of patients (n = 882). The mean disease duration in this subcohort was 5.0 (IQR 2.0-14.0) years (18). A total number of 540 patients died during the study period. The relative number of patients that died during the study period was 45% (540/1213). We expected based on the mortality rates of the general population that 29% (352/1213) would have died during the study period (Table 1).

All-cause mortality

The estimated SMR (95% confidence interval) for all-cause mortality was 1.54 (1.41, 1.67) over the period of 15 years. This indicates a 54% higher risk of mortality compared with the general Dutch population. In women, it was 1.62 (1.46, 1.80), and in men, it was 1.32 (1.13, 1.55).

The partial life expectancy for the Dutch population for the same period of 15 years was 13.4 years. The corresponding life expectancy for the RA cohort was 12.2 years. The number of expected life-years the RA cohort lost compared with the general population during the study period was 1.2 years.

Table 1. Number of observed deaths for each year of the study period

Year	N	Total	Percentage
1997	19	1213	1,57
1998	41	1194	3,43
1999	43	1151	3,74
2000	38	1113	3,41
2001	43	1070	4,02
2002	45	1025	4,39
2003	35	990	3,54
2004	38	952	3,99
2005	42	910	4,62
2006	37	873	4,24
2007	35	838	4,18
2008	21	817	2,57
2009	38	779	4,88
2010	21	758	2,77
2011	21	737	2,85
2012	23	714	3,22

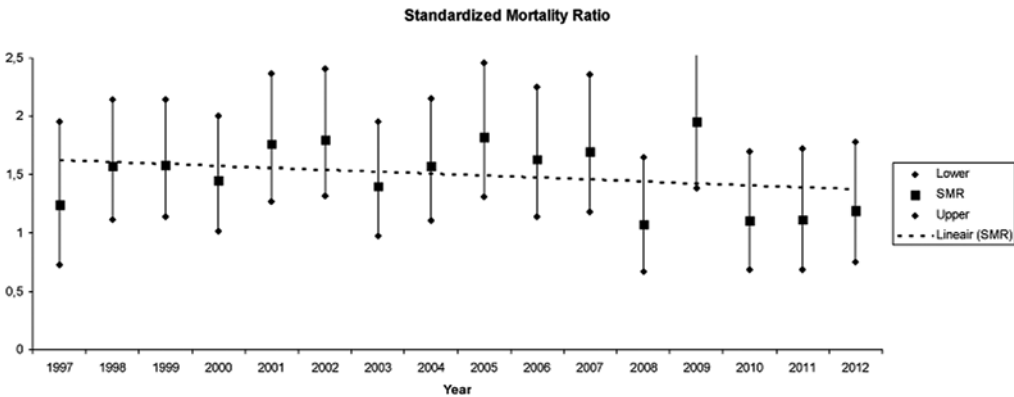


Figure 1: Annual Standardized Mortality Ratio and 95% confidence interval

Table 2: All-cause mortality in RA population

Table 2a: SMR (mean 3 years)	Confidence Interval			Confidence Interval			Confidence Interval		
	Men	Lower	Upper	Women	Lower	Upper	Total	Lower	Upper
1997-2000	1.42	0.72	2.50	1.63	1.07	2.37	1.54	1.08	2.14
2001-2003	1.29	0.64	2.31	1.80	1.21	2.57	1.65	1.19	2.24
2004-2006	1.57	0.82	2.71	1.75	1.14	2.57	1.68	1.20	2.30
2007-2009	1.45	0.69	2.70	2.07	1.36	3.01	1.58	1.07	2.24
2010-2012	0.76	0.25	1.82	1.56	0.96	2.42	1.14	0.71	1.73
Table 2b: SMR (mean 5 years)									
1997-2002	1.49	0.78	2.58	1.66	1.07	2.44	1.63	1.15	2.22
2003-2007	1.36	0.67	2.46	1.75	1.15	2.55	1.63	1.15	2.24
2008-2012	1.02	0.39	2.17	1.42	0.85	2.24	1.29	0.83	1.91
Table 2c: SMR (mean 15 years)									
1997-2012	1.32	1.13	1.55	1.62	1.46	1.80	1.54	1.41	1.67

SMR = Standardized Mortality Ratio, adjusted for age and gender

Table 3: Cause-specific mortality in rheumatoid arthritis population (N = 535) over 15 years (1997-2012)

	Observed	Expected	SMR	Confidence Interval	
				Lower	Upper
Circulatory system diseases	172	140	1.23	1.05	1.43
Neoplasms	112	108	1.03	0.85	1.24
Respiratory system diseases	62	44	1.42	1.09	1.82
Musculoskeletal and connective tissue diseases	49	3	17.4	12.85	22.97
Digestive system diseases	29	16	1.79	1.20	2.57
Mental & behavioural disorders	23	22	1.04	0.66	1.57
Abnormal clinical & laboratory signs not elsewhere classified	20	18	1.09	0.66	1.68
External causes of morbidity and mortality	17	11	1.55	0.90	2.48
Endocrine, nutritrial, & metabolic diseases	14	14	1.01	0.55	1.69
Infections	10	5	1.90	0.91	3.50
Nervous system diseases	10	12	0.86	0.41	1.57
Genitourinary system, skin, & subcutaneous tissue, and blood & blood forming organs diseases	17	13	1.29	0.75	2.06

SMR = standardized mortality ratio, adjusted for age and sex

Change in all-cause mortality

Figure 1 shows the annual SMR. Table 2 shows the mean SMR for all-cause mortality over 3 years, over 5 years, and over the total study period. The outcome of the regression analysis showed that there was a trend to decreasing SMR (2% annually, $p = .07$).

Cause-specific mortality

The most frequent causes of death for the RA cohort were circulatory system diseases (32%), neoplasms (21%), and respiratory system diseases (12%). Table 3 shows the SMR for all causes of death compared with the general Dutch population. The RA cohort mortality was higher for circulatory system diseases, respiratory system diseases, musculoskeletal system diseases, and digestive system diseases ($p < .05$).

DISCUSSION

This 15-year study showed that the mortality in patients with RA is still higher than that of the general population, but seems to decrease over time. Mortality was higher for circulatory-, respiratory-, musculoskeletal-, and digestive system diseases.

Patients with RA had a 54% higher risk of mortality compared with the general population. This shows that excess mortality in RA still occurs and that the overall mortality rate is still as high as it was in the past decades (1,34).

The number of life-years lost during the 15-year study period compared with the general population was about 1 year. The mean age at baseline was 60 years and the 15 year follow-up period is, roughly, half the period needed to observe the full life expectancy. Under this assumption this results in the estimated total number of life-years lost being of two years for a 60-year-old patient.

Likewise, the mortality ratio tended to decrease over time. This is underscored by the fact that the mortality ratio in the last 3 years of the study period was lower than in the preceding years and comparable to that of the general population. This trend towards a decrease in mortality might reflect the introduction of more intensive treatment in the last two decades. Other explanations for the decreasing mortality in this study might be that this cohort that was studied was a fixed cohort, hence new patients could not enter the study. As a result, the improved mortality could be a survival effect, in which patients with more “severe” RA died at the start of the study period (for example patients with shorter disease duration or with rheumatoid factor positive) and less “severe” patients survived and were followed up to the end of the study, which resulted in lower SMR at the end of the study period. We were able to study the association between disease duration and mortality (adjusted for age and sex) in a subcohort of 882 patients. There was no association between disease duration and mortality, which makes it more plausible that adjusting for disease duration would not have changed our results (data not shown).

Cause-specific mortality was determined through the primary cause of death. This study showed that musculoskeletal and connective tissue diseases were the primary cause of a high number of deaths. Our results differ from other studies, which report that RA is the primary cause of death in only a few cases (38). This might be due to the definition used by Statistics Netherlands. In their databank, the primary cause of death is defined as the underlying cause of death or the disease that started a sequence of incidents that resulted in death (39). The primary cause of death in the category musculoskeletal and connective tissue diseases was mostly RA and other types of arthritis. The secondary cause of death in patients who were classified as having a musculoskeletal and connective tissue disease as primary cause of death was injury, poisoning, and certain other consequences of external causes in 20%, circulatory diseases in 16%, respiratory diseases in 16%, and infections in 12% of the cases (data not shown). Different definitions of cause of death, used in national registries, will have important implications for study results. Therefore, results addressing cause-specific mortality, originating from different national registries, should be interpreted with caution.

Causes of death that were higher compared with the general population were diseases of the circulatory-, respiratory-, musculoskeletal- and digestive system. The change in health care could have resulted in different causes of death.

It is expected that current tight disease control translates into a lower CV mortality. Results of this study showed that the majority of the patients died due to CV diseases, which appeared to be the primary cause of death in 32% of the cases. This is somewhat lower than reported in older studies (conducted before implementation of intensive treatment and tight control of disease) where 40% of the patients with RA died due to CV diseases (34). Our lower CV death rate might be related to currently applied medications. Nevertheless, it is still significantly higher than in the general population.

Mortality due to respiratory disease was also higher in the RA cohort compared with the general population. Although we did not look in detail to which specific respiratory diseases were registered in our cohort, other literature suggests that in most cases this will be respiratory infection (5). The use of biologicals is associated with more severe infections (35-37) and therefore it is expected that mortality due to respiratory disease would be higher than in the general population.

In our study, infection as a cause of death was not higher than that of the general population, while other studies report a higher incidence (34). Infection was, however, often the secondary cause of death when RA was the primary cause of death. Adding the number of patients with infection as a secondary cause of death to the number of patients with infection as a primary cause of death resulted in a significantly higher cause-specific mortality ratio for infection (data not shown).

This is the first Dutch study reporting SMRs until 2012 and the first Dutch study reporting the number of life-years lost in a well-defined cohort of patients with

established RA. Moreover, the high number of deaths made it possible to study the cause specific SMRs for a wide range of causes of death. Another strength of this study was that 99% of the patients could be linked to the Municipal Register of the Statistics Netherlands. Furthermore, this study was conducted in a period in which the treatment of patients with RA changed (focus on tight disease control with the use of high dose DMARDs from the 1990s and biologicals from 2000), which made it possible to investigate the effect of the new medication. However, a limitation of the study was that no comparisons could be made between the mortality in the study population and the general population corrected for confounders, such as use of medication, smoking, autoantibody profile, and structural damage, because data addressing all these confounders were not available.

In this study, the mortality rate was calculated using indirect standardization. An advantage of indirect standardization is that only information about the total number of deaths for each year in the study population is needed. Thus, the standardized mortality rate can be calculated even if age-specific death rates of the study population at issue are not available or if the number of deaths for each age group is small (40). A disadvantage is that it represents mortality for an age and sex distribution similar to the study population at issue. By comparing SMRs between studies, it is important to keep in mind that differences in SMRs can be caused by differences in age or sex distribution between study populations at issue.

Comparing the mortality in our RA cohort with the mortality in the general Dutch population may result in selection bias if the RA cohort does not represent the national patient population because of regional differences. However, all patients in this study were recruited from outpatient clinics which have patients referred both from Amsterdam and the northwest part of the Netherlands. Although the mortality in Amsterdam is higher than the mortality in the general Dutch population, the mortality in Amsterdam combined with the northwest part of the Netherlands is comparable to the general Dutch population (41). For future research, however, we recommend to study the mortality in a RA cohort origination from a national registry.

Clinical relevance

In patients with established RA the mortality risk is still higher than the mortality in the general Dutch population, with more than a life-year lost over a period of 15 years. As the primary cause of death is mostly CV disease screening for and providing information about CV diseases (and CV risk factors) in the rheumatology practice are important. On the other hand the decrease in mortality coincided with changes in medication policy. Hence, tight disease control is also important to lower the high mortality risk in RA.

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Chapter 5

Association of somatic comorbidities and comorbid depression with mortality in patients with rheumatoid arthritis: a 14-year prospective cohort study

J van den Hoek, HC Boshuizen, LD Roorda, GJ Tijhuis, MT Nurmohamed, J Dekker, GAM van den Bos. Association of somatic comorbidities and comorbid depression with mortality in patients with rheumatoid arthritis: a 14-year prospective cohort study. *Arthritis Care and Research (Hoboken)* 2016; 68: 1055-60.

ABSTRACT

Introduction. Patients with rheumatoid arthritis (RA) have a significantly increased risk of mortality compared with the general population. One of the most important predictors for mortality is somatic comorbidity. Moreover, studies have demonstrated that comorbid depression is associated with mortality. Which specific comorbidities are associated with mortality is less investigated. The purpose of this study was to investigate the association of a wide range of comorbidities with mortality in patients with RA.

Methods. Longitudinal data over a 14-year period were collected from 882 patients with RA. Data were assessed with questionnaires. The mortality status was obtained from the Statistics Netherlands for the period 1996-2011 for 99% of the patients. Somatic comorbidity was assessed in 1997, 1998, 1999 and 2008 and measured by a national population-based questionnaire including 20 chronic diseases. Comorbid depression was assessed in 1997, 1998 and 1999 and measured with the Center for Epidemiologic Studies Depression Scale. Cox regression was used to study the relationship between comorbidity and mortality.

Results. At baseline, 72% of the patients were women. The mean age \pm SD was 59.3 \pm 14.8 years and the median (interquartile range) disease duration was 5.0 (2.0-14.0) years. A total of 345 patients died during the study period. Comorbidities that were associated with mortality were circulatory conditions (hazard ratio [HR] 1.60 [95% Confidence Interval (95% CI) 1.15-2.22]), respiratory conditions (HR 1.43 [95% CI 1.09-1.89]), cancer (HR 2.00 [95% CI 1.28-3.12]) and depression (HR 1.35 [95% CI 1.06-1.72]).

Conclusion. Comorbid circulatory conditions, respiratory conditions, cancer, and depression are associated with mortality among patients with RA. Careful monitoring of these comorbidities during the course of the disease and adequate referral may improve health outcomes and chances of surviving.

INTRODUCTION

Patients with rheumatoid arthritis (RA) have a significantly increased risk of mortality (1-3) in comparison with the general population. Although the management of RA improved in the last decades, the survival in patients with RA has not improved to the same degree as that of the general population (4,5). Analyses of trends in RA mortality over time revealed 3 lines of evidence: systemic inflammation in RA may promote comorbidity, patients with RA have more serious comorbid conditions, and patients with RA may not receive optimal care for their comorbidities (6). A review about mortality in RA showed that comorbidities are one of the most significant predictors for mortality (7).

Which specific comorbid conditions are associated with mortality has less been investigated. Some studies evaluated a limited number of comorbid conditions (8,9). However, studying a wide range of comorbid conditions is needed to obtain a more comprehensive view and to provide clinically useful tools for optimizing care. One study investigated the association of a wide range of comorbid conditions with mortality (10) and found cancer and dementia as most highly associated with mortality. However, that study was conducted more than a decade ago.

The most important causes of death among patients with RA are: cardiovascular diseases, respiratory diseases, digestive diseases, hematologic diseases, infectious diseases and malignancies (11). However, the causes of death do not have to correspond with the preexisting comorbid conditions that are longitudinally associated with mortality. Preexisting comorbidities are a possible target of disease management.

A few studies found that comorbid depression was associated with mortality. One study found comorbid depression to be a predictor for all-cause mortality (12). Another study among veterans with RA also found depression to be a predictor for myocardial infarction (13). Depressed patients with RA were 40% more likely to have a myocardial infarction than non-depressed patients in that study.

The aim of this study was therefore to investigate a wide range of comorbidities, including comorbid depression, and which conditions are associated with mortality. Evaluating the relative contribution of specific comorbidities will provide valuable information for clinical practice and the management of patients with RA.

PATIENTS AND METHODS

Study design and population

In 1997, our research group started a longitudinal study on comorbidity and health outcomes in patients with RA (14). A sample of 1251 patients was randomly selected from the register of a large rheumatology outpatient clinic in Amsterdam, which included the patients from 7 allied outpatient clinics. For inclusion in the study, patients had to fulfill the following eligibility criteria: a diagnosis of RA according to the American College of Rheumatology Criteria for RA (15), ages ≥ 16 years, adequate knowledge of the Dutch language, and at least 1 visit to a rheumatologist in the previous 2 years.

Data were collected in 1997, 1998, 1999, 2002 and 2008 by means of self-administered questionnaires (16). The questionnaires comprised questions about sociodemographic characteristics (age, sex, marital status, educational level and employment status), clinical characteristics (including comorbidity), health characteristics, and the use of health care services. Information on disease duration was retrieved from the patients' medical records, and disease activity was assessed during clinical examination at baseline. All participants provided written informed consent. The study was approved by the Reade/Slotervaart Institutional Review Board.

Measurements

Mortality

All participants who participated in the study at baseline were linked to the mortality records during the period 1996–2011 from the Register of the Statistics Netherlands (17). For patients who could not be linked to these records, data were obtained from the outpatient clinic register.

Comorbidity

Somatic comorbidity was assessed in 1997, 1998, 1999 and 2008. Somatic comorbidity was measured with a list adapted from the Health Interview Survey of the Statistics Netherlands (18), a validated list amenable to self-reporting (19). This list covers 20 chronic conditions that are relatively prevalent in The Netherlands. Respondents were asked to indicate whether they had had any of the conditions in the previous 12 months. The following 9 categories of chronic somatic comorbidity were created based on the body systems involved: circulatory conditions (myocardial infarction or other serious heart disorders, stroke), respiratory conditions (asthma or chronic bronchitis), digestive conditions (disorders of the stomach, disorders of the liver, disorders of the gall bladder or serious disorder of the intestine longer than 3 months, genitourinary conditions (disorders of the kidneys, kidney stones, inflammation of the bladder, neurological conditions (migraine, dizziness with falling, epilepsy, musculoskeletal

conditions (herniated disc or chronic back), endocrine, metabolic and nutritional conditions (diabetes mellitus or disorders of the thyroid gland), cancer, and an additional category (hypertension, infection of the nasal cavity or frontal sinus, or skin conditions). This classification was in accordance with previous research also using the list about somatic comorbidity from the Health Interview Survey of the Statistics Netherlands (20).

Comorbid depression was assessed in 1997, 1998 and 1999. Comorbid depression was assessed with the Centre for Epidemiological Studies-Depression Scale (CES-D) (21). The CES-D is a short self-administered scale designed to measure depressive symptomatology in the general population. The CES-D consists of 20 items and has a range of 0 to 60, with higher scores indicating more depressive symptomatology. Scores of ≥ 16 suggest presence of depression.

Control variables

The control variables included age, sex, socioeconomic status (SES), disease duration and disease activity. SES was indicated by educational level. We divided SES into 3 categories: low SES, indicating patients with no education or education at the primary school level, medium SES, indicating patients with education at the secondary school level, and high SES, indicating patients with a college or university level education. Disease activity was assessed by means of the Disease Activity Score in 28 joints (DAS28), separately scoring swelling and tenderness of 28 joints (and without using the visual analogue scale for general health assessment (22).

Statistical analyses

Participants with complete and incomplete followup were compared for statistical significant differences in baseline variables with chi-square tests and t-tests. To study the relationship between comorbidity and survival among patients with RA, we performed a Cox regression analysis. The variable 'comorbidity' was added to all models as a time-varying covariate linking the comorbidity to time. This linking means that the last measured comorbid condition was applied. We first performed univariate analyses for each category of comorbidity, adjusted for age and sex. Secondly, we performed a multivariate analysis with all categories of comorbidity in the model. Depression was added to the model as a dichotomous variable (CES-D score < 16 versus CES-D score ≥ 16). All models were adjusted age, sex, SES, disease duration, and disease activity. In order to investigate whether the level of depression is associated with mortality risk, a multivariate analysis with the same model was performed. In this additional multivariate analysis, depression was added to the model as a continuous variable (continuous CES-D score). The hazard ratio (HR) resulting from the Cox regression analysis should be interpreted as the proportional change

Table 1. Description of rheumatoid arthritis (RA) study population at baseline (n=882)

Sex		
Men	248	(28.1)
Women	634	(71.9)
Age, mean ± SD years	59.3	± 14.8
Disease duration, median (IQR) years	5.0	(2.0-14.0)
Disease activity (DAS28), mean ± SD	3.6	± 1.3
Physical functioning (HAQ), mean ± SD	1.14	± 0.80
Comorbid conditions, categories		
Circulatory	49	(5.6)
Respiratory	117	(13.3)
Digestive	84	(9.5)
Genitourinary	43	(4.9)
Neurologic	91	(10.3)
Musculoskeletal, other than RA	121	(13.7)
Endocrine, metabolic and nutritional conditions	82	(9.3)
Cancer	18	(2.0)
Other	274	(31.1)
Depression	251	(28.5)

Values are the number (%) unless indicated otherwise. IQR = interquartile range;
DAS28 = Disease Activity Score in 28 joints; HAQ = Health Assessment Questionnaire.

Table 2. Association of specific comorbidities and mortality in patients with rheumatoid arthritis (RA) (n=882)

	Univariate analyses ¹			Multivariate analysis ²		
	HR	(95%CI)	P	HR	(95%CI)	P
Circulatory conditions	1.67	(1.23 - 2.26)	0.001	1.60	(1.15 - 2.22)	0.006
Respiratory conditions	1.51	(1.17 - 1.95)	0.002	1.43	(1.09 - 1.89)	0.011
Digestive conditions	1.59	(1.10 - 2.30)	0.015	1.46	(0.99 - 2.15)	0.058
Genitourinary conditions	1.02	(0.68 - 1.54)	0.921	0.89	(0.59 - 1.36)	0.595
Neurologic conditions	0.95	(0.70 - 1.28)	0.725	0.77	(0.56 - 1.07)	0.123
Musculoskeletal conditions other than RA	0.96	(0.72 - 1.27)	0.774	0.93	(0.69 - 1.25)	0.618
Endocrine, metabolic and nutritional conditions	1.13	(0.82 - 1.55)	0.451	1.00	(0.71 - 1.40)	0.986
Cancer	2.20	(1.43 - 3.40)	<0.001	2.00	(1.28 - 3.12)	0.002
Other conditions	0.95	(0.76 - 1.18)	0.616	0.81	(0.64 - 1.03)	0.081
Depression	1.47	(1.18 - 1.83)	0.001	1.35	(1.06 - 1.72)	0.016

HR = Hazard ratio; 95% CI = 95% confidence interval.

1 Outcome of Cox regression analyses, with comorbidity as time-varying covariate, and adjusted for age and sex

2 Outcome of Cox regression analysis, with comorbidity as time-varying covariate, and adjusted for age, sex, socioeconomic status, disease duration, disease activity and all other comorbidities

in the risk of mortality associated with the comorbidity at issue. All analyses were carried out using SPSS software, version 14.0. Results were considered statistically significant when *P* values were less than 0.05.

RESULTS

Response

Of the eligible patients, 882 (76%) returned the questionnaire in 1997 (16). Of these patients, 755 (crude response 85%, net response [the response in patients not deceased] 87%) returned the questionnaire in 1998, 683 (crude response 77%, net response 81%) in 1999, 529 (crude response 60%, net response 71%) in 2002 and finally, 370 (crude response 42%; net response 62%) returned the questionnaire in 2008. Patients with incomplete followup were older, had longer disease duration, higher baseline DAS scores, lower baseline physical functioning and more often had circulatory problems, respiratory conditions and cancer, compared with patients with complete followup. Of the 1251 patients that were selected at baseline, 1237 (99%) could be linked to the Municipal Register at Statistics Netherlands, 5 patients deceased according to the outpatient clinic register. For 9 patients no information about mortality could be obtained. Of the 882 patients that responded at baseline, 876 could be linked to the Municipal Register at Statistics Netherlands, 4 patients were found in the register of the outpatient clinic and 2 patients were excluded from the analyses, because no mortality data were available. The number of patients that deceased during the study period was 345.

Study population

Baseline patient characteristics are summarized in Table 1. Of all patients at baseline, 72% were women, the mean ± SD age was 59.3 ± 14.8 years and the median (interquartile range) disease duration was 5.0 (2.0-14.0) years.

Association of specific comorbidities and mortality

Table 2 shows the results of the Cox regression analyses investigating which comorbid conditions are associated with mortality. Univariate analyses showed that circulatory conditions, respiratory conditions, digestive conditions, cancer, and depression were associated with mortality (*P* < 0.05). In the multivariate model, circulatory conditions, respiratory conditions, cancer, and depression were associated with mortality. Using the continuous CES-D score resulted in an increased risk of mortality of 2% with each point of increase on the CES-D score (HR 1.02, *P* =0.007). Diagnostics of collinearity between the categories of comorbidity showed that collinearity was not an issue.

DISCUSSION

Data from this large prospective cohort study showed that circulatory conditions, respiratory conditions, cancer, and depression were associated with mortality. This finding provides valuable information for clinicians, because they could possibly treat these comorbidities.

The association of somatic comorbidity with mortality has been previously described in the literature (7). However, in these studies, comorbidity is usually measured with a dichotomous score (23), a sum score (24) or an index score (25), while clinical practice asks for simply recording the presence or absence of a specific comorbid condition (26). To our knowledge only 1 other study investigated the association of a wide range of comorbidities with mortality (10) and found partly the same associated comorbidities. However, in that study, data collection of the inception cohort took place between 1955 and 1994, while in our study data collection started in 1997 and included patients with RA with a median disease duration of 5 years. Our cohort was likely treated with modern medication for RA and possibly also for comorbidities.

In this study patients with incomplete followup were older, were had longer disease duration, higher baseline DAS scores and lower baseline physical functioning. This finding implies that more severe patients dropped out of the study, often the patients with more severe comorbidities. Therefore, the relationship between the specific comorbidities and mortality might be stronger than this study suggest.

A remarkable result was the association of comorbid depression with mortality.

In the multivariate analysis, depression was added to the model as a dichotomous score, which implies that depression was identified by the CES-D cutoff of ≥ 16 . Using the continuous score of the CES-D, in the additional multivariate analysis, resulted in an even higher risk for mortality, with 2% increased risk with each point increase for depression on the CES-D. This result means that a patient with the maximum score in our cohort of 41 has a $(1.02)^{41} = 2.25$ increased risk of mortality, compared with a patient with the minimum score of zero. This finding emphasizes even more the importance of depression in patients with RA. In this cohort, the duration of depression, or being depressed at more than one time point, did not result in an increased mortality risk (data not shown).

A study of Ang et al (12) found comorbid depression to be an independent risk factor for mortality in RA. Little is known about the mechanisms that account for the association between comorbid depression and mortality. Depression may increase the risk of mortality through several factors (27). However, this relationship is complex.

The major strengths of our study were its longitudinal design, its long-term followup period, the large patient sample, the relatively high response rate during the followup period and the mortality data that could be obtained for almost all patients. Another strength of the study is that not only baseline comorbidity scores were used

to determine the association with mortality, but that comorbidity was measured at 4 time points during the 14-year followup period. In the statistical model, the comorbidity was updated over time. A few study limitations have to be considered. In our study, information about comorbidity was self-reported and patients were asked whether they had had a comorbid condition in the past 12 months, which may have led to underestimation of comorbidity. For example, patients who had a myocardial infarction 5 years previously and were taking medication for the condition could consider themselves as not having cardiovascular comorbidity. However, the list that was used has been validated (19).

Depression was measured with a self-reported questionnaire. Studies investigating prevalence of depression in RA populations show that the prevalence of depression is higher when measured with self-reported measurement instruments than when diagnosed by psychiatric interview (28). The depression measured should therefore be interpret as a possible depression (21). To our knowledge, the association between depression measured by interview and mortality has never been investigated in patients with RA. Future research should establish if measuring depression by diagnostic interview changes the association between depression and mortality in patients with RA.

In addition, somatic comorbidity was recorded at 4 time points of measurement, while comorbid depression was measured at 3 time points. This difference could have led to less accurate measurement of comorbid depression compared to somatic comorbidity. However, an additional analysis, with 3 time points of measurement for somatic comorbidity, did not result in different conclusions with respect to the relationship between comorbidities and mortality (data not shown).

This study was initially designed to study health outcomes in patients with RA. Therefore, potential clinical confounders such as body mass index, cholesterol and blood pressure were not collected, which could have resulted in an overestimation of the risk of depression.

Our results highlight the importance of specific comorbidities, in relation to mortality, for daily clinical practice. We do not have information with respect to the adequacy of the treatment that participants received for their comorbidities. However, it has been suggested that patients with RA are better treated for their arthritis than for their comorbid conditions (29, 30). For example, underdiagnosis of depression by general practitioners occurs frequently among patients having chronic somatic diseases (20). We recommend that clinicians place greater emphasis on comorbid conditions in patients with RA. How to implement such a recommendation in daily clinical practice will depend on the structure of the health care system at hand. In The Netherlands, this recommendation could necessitate an important role for rheumatologists, in signaling and underlining the importance of their comorbid conditions to the patient, and for the general practitioners in monitoring, referring and coordinating care. Assessing

comorbidity and adequate disease management for comorbidity are crucial parts of the clinical evaluation and treatment of patients with RA. Clinical practice guidelines should incorporate clinically relevant comorbidities to optimize care and ultimately reduce mortality.

Comorbid circulatory conditions, respiratory conditions, cancer, and depression are associated with mortality among patients with RA. Careful monitoring of these comorbidities and adequate referral may improve health outcomes and chances of surviving.

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Chapter 6

Trend in and predictors for cardiovascular mortality in patients with rheumatoid arthritis over a period of 15 years: a prospective cohort study

J van den Hoek, LD Roorda, HC Boshuizen, GJ Tijhuis, J Dekker, GAM van den Bos, MT Nurmohamed. Trend in and predictors for cardiovascular mortality in patients with rheumatoid arthritis over a period of 15 years: a prospective cohort study. *Clinical and Experimental Rheumatology* 2016; 34: 813-19

ABSTRACT

Objectives. To investigate a) the cardiovascular (CV) mortality in a clinical cohort of patients with established rheumatoid arthritis (RA) in comparison with the general population over 15 years, b) the trend in this CV mortality during the study period, and c) for a broad range of predictors, which baseline variables predict CV mortality.

Methods. In 1997, a sample of 1222 patients was randomly selected from the register of a rheumatology outpatient clinic in Amsterdam. Their CV mortality between 1997 and 2012 was obtained from Statistics Netherlands. The Standardized Mortality Ratio (SMR) for CV mortality was calculated. A linear Poisson regression analysis was performed to investigate if there was a trend in SMR over time. A Cox regression analysis was performed to determine which baseline variables predicted CV mortality.

Results. Mean age of the population at baseline was 60.4 (*SD* 15.4) years and 72.6% of the patients were women. Estimated SMR (95% confidence interval) for CV mortality was 1.24 (1.05, 1.43). The SMR decreased with 3% annually ($p = .16$). Higher age, higher erythrocyte sedimentation rate, having CV comorbidity and Diabetes Mellitus (DM) were predictors for CV mortality.

Conclusion. CV mortality among patients with RA in the past 15 years was still higher than in the general population. CV mortality decrease was not statistically significant. As CV mortality in RA is still higher than in the general population, continued attention for CV diseases in RA is important. Both tight control of disease activity and good care for comorbid conditions (CV diseases and DM) are advocated.

INTRODUCTION

Patients with rheumatoid arthritis (RA) have a higher mortality risk compared with the general population (1). This higher mortality risk is mainly attributable to cardiovascular (CV) diseases (2-7). The CV mortality risk seems to be about 50% higher than in the general population (8). The higher CV mortality risk in RA is caused both by traditional CV risk factors (such as smoking, hypertension and dyslipidemia), which occur more frequent in patients with RA, and the underlying chronic inflammatory process (9-11). A population-based study in individuals from Northern Spain performed in the past decade disclosed that chronic inflammation, expressed by the mean C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) over and extended follow-up, was associated with increased cardiovascular mortality in patients with RA (12). Inflammation plays an important role in atherosclerosis and amplifies some traditional CV risk factors such as dyslipidemia, obesity and insulin resistance (13-16). Besides traditional CV risk factors and chronic inflammation, a genetic component may also explain the increased rate of CV disease observed in patients with RA (12,17).

Time trends in CV mortality have been studied less. Studies investigated trends in all-cause mortality (18-20). However, only one meta-analysis investigated the trend in CV mortality between 1945-1995 and found no change in CV mortality rate (21). Nevertheless, recent years have witnessed the introduction of tight disease control and of more intensive treatment consisting of high dose treatment with disease-modifying antirheumatic drugs (DMARDs) from the 1990s onwards and the introduction of biologicals after 2000 (22,23). Moreover, the increased CV risk in patients with RA is nowadays widely acknowledged and thus the need for CV risk management (24,25). These improvements in medical care may have resulted in lower CV mortality.

Demographic as well as clinical and functional variables predict CV mortality. Age, sex and socioeconomic status (SES) predict CV mortality both in the general population and in patients with RA (9). Likewise, disease activity markers (ESR, CRP level and Disease Activity Score in 28 joints (DAS28)) (2,10,26), disease duration (27), comorbidities (CV disease, hypertension, diabetes mellitus (DM)) (9,10) and physical functioning predict CV mortality in RA (7,26). Until now, the impact of these variables on CV mortality has been studied separately and not in combination. A EULAR task force for CV risk management noted this unmet need and advocated to study for a broad range of variables the combined contribution (demographic- as well as inflammatory- and traditional risk factors) to CV mortality in patients with RA in large prospective cohort studies (24).

The aims of this study were a) to investigate the CV mortality in a clinical cohort of patients with established RA in comparison with the general population over 15 years, b) to study the trend in CV mortality in these patients during the study period, c) to investigate for a broad range of predictors, whose baseline variables predict CV mortality in patients with established RA.

PATIENTS AND METHODS

Study design and population

In 1997, our research group started a cohort study on health outcomes in patients with RA (28). A sample of 1222 patients was randomly selected from the register of a large rheumatology outpatient clinic in Amsterdam, which included the patients from seven allied outpatient clinics. For inclusion in the study, patients had to fulfil the following eligibility criteria: a) being diagnosed with RA according to the American College of Rheumatology (ACR) Criteria for RA (29), b) being 16 years of age or older, c) having sufficient command of the Dutch language, d) having visited a rheumatologist at least once in the previous 2 years.

Data were collected by means of self-administered questionnaires (30), which comprised questions about socio-demographic characteristics (age, sex, marital status, educational level, employment status and living situation), clinical characteristics (pain, comorbidity), functional characteristics (disability and quality of life), health characteristics and the utilization of health-care services. In addition, with respect to the clinical characteristics, information on disease duration and rheumatoid factor were retrieved from the patients' medical records, and disease activity was assessed during clinical examination at baseline. All participants provided written informed consent. The study was approved by the Reade/Slotervaart Institutional Review Board.

Measurements

Cardiovascular mortality

All patients were linked to Statistics Netherlands' mortality records for the period 1997-2012 (31). The Statistics Netherlands' databank provides death/life status, death dates, and primary and secondary causes of death. We used the primary cause of death of the category 'diseases of the circulatory system' (31). The primary cause of death is defined as the underlying cause of death, which started a sequence that finally resulted in death. The linkage of the patients to the mortality data was anonymous, using only date of birth, sex, and, if available, civil registration number, and was performed by staff of Statistics Netherlands (32). In order to compare patients with the general population,

age and sex specific CV mortality data for the general population were provided by Statistics Netherlands (33).

Predictors

Sociodemographic, clinical and functional variables were investigated. Variables were selected which are known to be associated with CV mortality (2,9,10,26) or all-cause mortality in patients with RA (7,34-36).

Sociodemographic variables

The sociodemographic variables included age, sex and SES. SES was indicated by educational level. We divided SES into 3 categories: low SES (no education or education at the primary school level), medium SES (education at the secondary school level), and high SES (college or university level education).

Clinical variables

The clinical measures include ESR, DAS28, disease duration, rheumatoid factor, pain, CV comorbidity, hypertension and DM. Disease activity was assessed by means of the ESR and the DAS28, scoring separately swelling and tenderness of 28 joints (and without using the visual analogue scale for general health assessment). Disease duration was computed using the date of RA diagnosis, which was retrieved from the patients' medical record. Information about rheumatoid factors was abstracted from the patients' records. Pain was measured with the Visual Analogue Scale (VAS), ranging from no pain at all to pain as bad as it could be. CV comorbidity, hypertension and DM were measured with a self-report list adapted from the Health Interview Survey of Statistics Netherlands, a validated list amenable to self-reporting (37). Patients were asked to indicate whether they had had the condition in the previous 12 months. CV comorbidity included myocardial infarction, any other serious heart disorders, or stroke. Respondents indicating the presence of at least one or more conditions were classified as having CV comorbidity.

Functional variables

Physical functioning was measured with the validated Dutch version of the Health Assessment Questionnaire (HAQ) and the physical scales of the Dutch version of the RAND-36 (38). The HAQ category score was raised when aids or devices were indicated by the patient. Mental functioning was measured with the mental scales of the Dutch version of the RAND-36. A Physical Component Scale (PCS) and a Mental Component Scale (MCS) were calculated according to the manual for SF-36 health summary scales (39), using Dutch population means, standard deviations and factor score coefficients (40).

Statistical analyses

The standardised mortality ratio (SMR) was computed to compare the CV mortality in the RA cohort with the general population. The SMR is the ratio of the number of observed deaths in a study population divided by the number of expected deaths in the case where the study population would have had the same age, sex, and calendar year specific mortality rates as the general population. We calculated the SMR for CV mortality, for each year, the mean of 3 years, the mean of 5 years, and the mean of all 15 years. Ninety-five percent confidence intervals were calculated using Byar's approximation.

Linear Poisson regression analysis was performed to determine if there was a trend towards an increase or decrease in the SMR over time (38). The 1997 data were excluded from the calculation of the mean SMR and the regression analysis, because the precise date of inclusion in the cohort, and thus the amount of persontime in this year was not known.

To answer the first (CV mortality) and second research question (trend in CV mortality), the 1222 patients who were selected at baseline were linked to Statistics Netherlands. No information about CV mortality could be obtained for 14 patients and therefore, these patients were excluded. Hence, data of 1208 out of 1222 patients (99%) were used for the analyses.

To determine which baseline predictors were associated with CV mortality, we performed a Cox regression analysis. The outcome measure was CV mortality as primary cause of death (31). Patients who died from other causes of death were considered as censored. First, univariate analyses for each variable were performed. Second, variables

for a multivariate analysis were selected using backward selection excluding variables with p -values $>.05$. All models were adjusted for age and sex. Including multiple risk factors in the model increases the risk for multicollinearity. The only variables that were highly correlated were physical functioning measured with the HAQ and measured with the SF-36. Removing one of these variables from the model did not change the results. Multiple imputation was used to handle missing baseline values. All analyses were carried out using SPSS, version 20.0.

To answer the third research question (predictors for CV mortality) data of patients who responded to the questionnaire were used. A previous study in the same cohort investigated predictors for (non)response through a telephone interview of the nonrespondents. Patients who responded to the questionnaire reported less pain and were using more often additional health care than patients who did not respond, whereas ESR, disease duration, comorbidity and physical functioning were not different in both groups. Of the patients who were selected at baseline, 882 returned the questionnaire in 1997 and for this number of patients baseline predictor variables were available. Out of these 882 patients, 876 could be linked to the Statistics Netherlands and 6 patients were excluded from the analyses, because no mortality data was available

RESULTS

Study population

Mean age at baseline of the 1208 patients (first and second research question) was 60.4 (SD 15.4) years and 73% of the patients were women. A total number of 172 (out of 1208) patients died due to CV disease as the primary cause of death during the study period.

Mean age at baseline of the 882 patients (third research question) was 59.3 (SD 14.8) years, 72% were women, median disease duration was 5.0 (IQR 2.0-14.0) years, the mean DAS28 score was 3.6 (SD 1.3), and the mean HAQ score was 1.14 (SD 0.80) (Table 1). A total number of 117 (out of 876) patients died due to CV disease during the study period.

Cardiovascular mortality

The estimated SMR (95% confidence interval) for CV mortality was 1.24 (1.06, 1.45) over the period of 15 years, which indicates a 24% higher risk of CV mortality compared with the general Dutch population.

Trend in cardiovascular mortality

Figure 1 shows the annual SMR. Table 2 shows the mean SMR for CV mortality over 3 and 5 years intervals, and over the total study period. The outcome of the regression analysis showed that the SMR decreased with 3% annually, but the decrease did not reach statistical significance ($p = 0.16$).

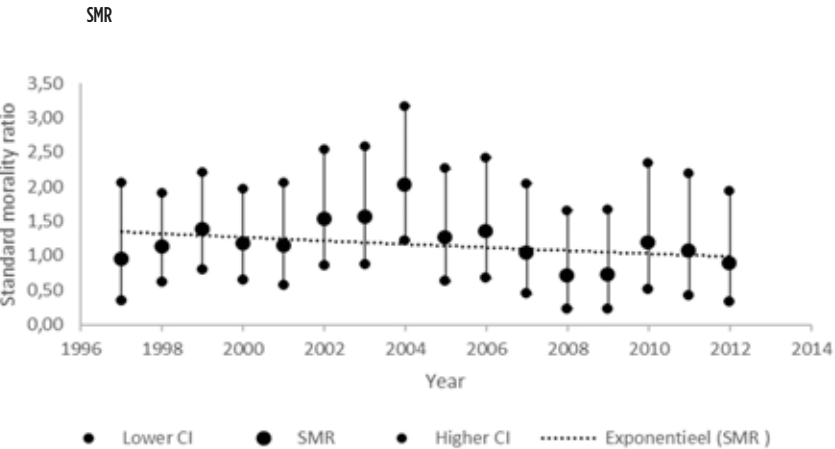


Figure 1. Trend in cardiovascular mortality

Predictors for cardiovascular mortality

Outcomes of the Cox Regression analyses showed that higher age, higher ESR, having CV comorbidity and DM were predictors for CV mortality (Table 3). Note that the hazard ratio for age and ESR is for each extra year and each extra mm/h respectively and the increased risk for comorbidity (CV and DM) is for patients having the comorbidity compared to patients not having the comorbidity.

Table 1. Baseline description of study population (n=882)

Sociodemographic variables			
Sex, no (%)	Women	634	(71.9)
	Men	248	(28.1)
Age, mean (SD)		59.3	(14.8)
Socioeconomic status, no (%)	Low	220	(24.9)
	Middle	526	(59.6)
	High	123	(13.9)
Clinical variables			
ESR (mm/h), mean (SD)		25.0	(19.8)
DAS28, mean (SD)		3.6	(1.1)
Disease duration (years), median (IQR)		5.0	(2.0-14.0)
Reumafactor, no (%)	Neg	331	(37.5)
	Pos	551	(62.5)
Pain (VAS), mean (SD)		40.6	(28.1)
Cardiovascular comorbidity, no (%)	No	833	(94.4)
	Yes	49	(5.6)
Hypertension, no (%)	No	702	(79.6)
	Yes	174	(19.7)
Diabetes mellitus, no (%)	No	833	(94.4)
	Yes	43	(4.9)
Functional variables			
Health Assessment Questionnaire, mean (SD)		1.1	(0.8)
SF-36, Physical Component Summary, mean (SD)		35.8	(10.8)
SF-36, Mental Component Summary, mean (SD)		49.2	(11.4)

SD = standard deviation, ESR = erythrocyte sedimentation rate, DAS28 = disease activity score of 28 joints, VAS = visual analog scale, SF-36 = 36-item short form health survey.

DISCUSSION

Results from this prospective cohort study showed that CV mortality in patients with established RA in the past 15 years was still higher than in the general Dutch population. CV mortality was determined through the primary cause of death. The primary cause of death is defined as the underlying cause of death, which started a sequence that finally resulted in death. Because RA was often indicated as the primary cause of death, the SMR for CV mortality using both primary and secondary cause of death was also computed. Nevertheless this did not change the conclusions (data not shown).

Although mortality rate seemed to decrease during the study period, this trend did not reach statistical significance. During the course of the study tight disease control, more intensive treatment and management of traditional CV risk factors have been introduced. We therefore expected to see a decrease in CV mortality rate (42). Probably not all patients were treated according to this policy from disease onset, because this was a cohort of patients with established RA, and the CV burden may already have been occurred. Thus the effect of intensive treatment on CV mortality may have been less effective than when intensive treatment started at disease onset. Moreover, also in the general population the management of traditional CV risk factors was further improved during the study period, which could explain why no decrease in CV mortality during the study period could be observed.

Table 2. Cardiovascular mortality in rheumatoid arthritis population for different time intervals

SMR (mean 3 years)	95% CI	
	Lower	Upper
1998-2000	1.23	0.69 2.03
2001-2003	1.42	0.77 2.39
2004-2006	1.57	0.85 2.64
2007-2009	0.83	0.30 1.80
2010-2012	1.05	0.42 2.15
SMR (mean 5 years)		
1998-2002	1.27	0.70 2.12
2003-2007	1.47	0.78 2.53
2008-2012	0.91	0.34 1.95
SMR (mean 15 years)		
1998-2012	1.24	1.06 1.45

CI = confidence interval, SMR = standard mortality ratio.

Some recent studies also investigating SMR of cardiovascular mortality found inconsistent results. One study, following patients with RA from disease onset, did not found an increase in CV mortality (43). Another study did found an increase in CV disease despite advances in RA disease management (44). A reason for the inconsistent results could be the different types of cohort and followup time (27).

Predictors for CV mortality were higher age, higher ESR, CV comorbidity and DM. These predictors were also reported in other studies (9,10).

In this study we used self-reported measurements of comorbidity. The questionnaire was tested for its validity in a separate study, whereby patients' self-reported data were compared with general practitioners' (GP) reported data derived from the medical record. The results of this validation study indicated that the agreement

between patient self-reported and GP reported was high especially for some diseases, including cardiovascular diseases (37). This study was initially designed to study health outcomes in patients with RA. Therefore, other important potential confounders such as smoking, body mass index and cholesterol were not investigated. In addition, we assessed variables at baseline only. For some variables, such as disease activity, annual assessments over time, allowing AUC calculations, could have contributed to predicting CV mortality. Baseline ESR turned out to be a strong predictor for CV mortality. We expect that further ESR assessments would have strengthened this relationship.

The strengths of this study were the large cohort and the use of recent mortality data. The high number of deaths made it possible to study the annual SMR for cardiovascular death and to study the trend in CV mortality. Another strength of this study was that 99% of the patients could be linked to the Statistics Netherlands' mortality records.

As CV mortality in RA is still higher than in the general population, continued attention for CV diseases in RA is important. Both tight control of disease activity and good care for comorbid conditions (CV diseases and DM) are strongly advocated. According to the EULAR recommendations for CV risk management, the CV risk estimate resulting from traditional CV risk factors should be multiplied by 1.5 when a patient with RA meets two or more of the following criteria: a disease duration of more than 10 years, RF or anti-CCP positively or the presence of severe extra-articular manifestations. The authors of these recommendations choose a conservative factor of 1.5, because most studies did not adjust for social- and economic variables, physical functioning, and stress (24). In the present study SES, physical functioning and mental functioning were included in the model. Patients with a high disease activity had increased risk of CV mortality, whereby the risk increased with 2% for each mm/h. These results can be converted in a risk score for a patient with a disease activity of ≥ 30 mm/h. For patients above this cut off point the risk of CV mortality is increased with 80%. Our results do not support the conservative approach (factor 1.5 instead of 1.8) from the EULAR recommendations for patients with high disease activity. In conclusion, the CV mortality among patients with RA in the past 15 years was still higher than in the general population and did not decrease statistically significant. Both tight control of disease activity and good care for comorbid conditions are advocated.

Table 3. Predictors for cardiovascular mortality.

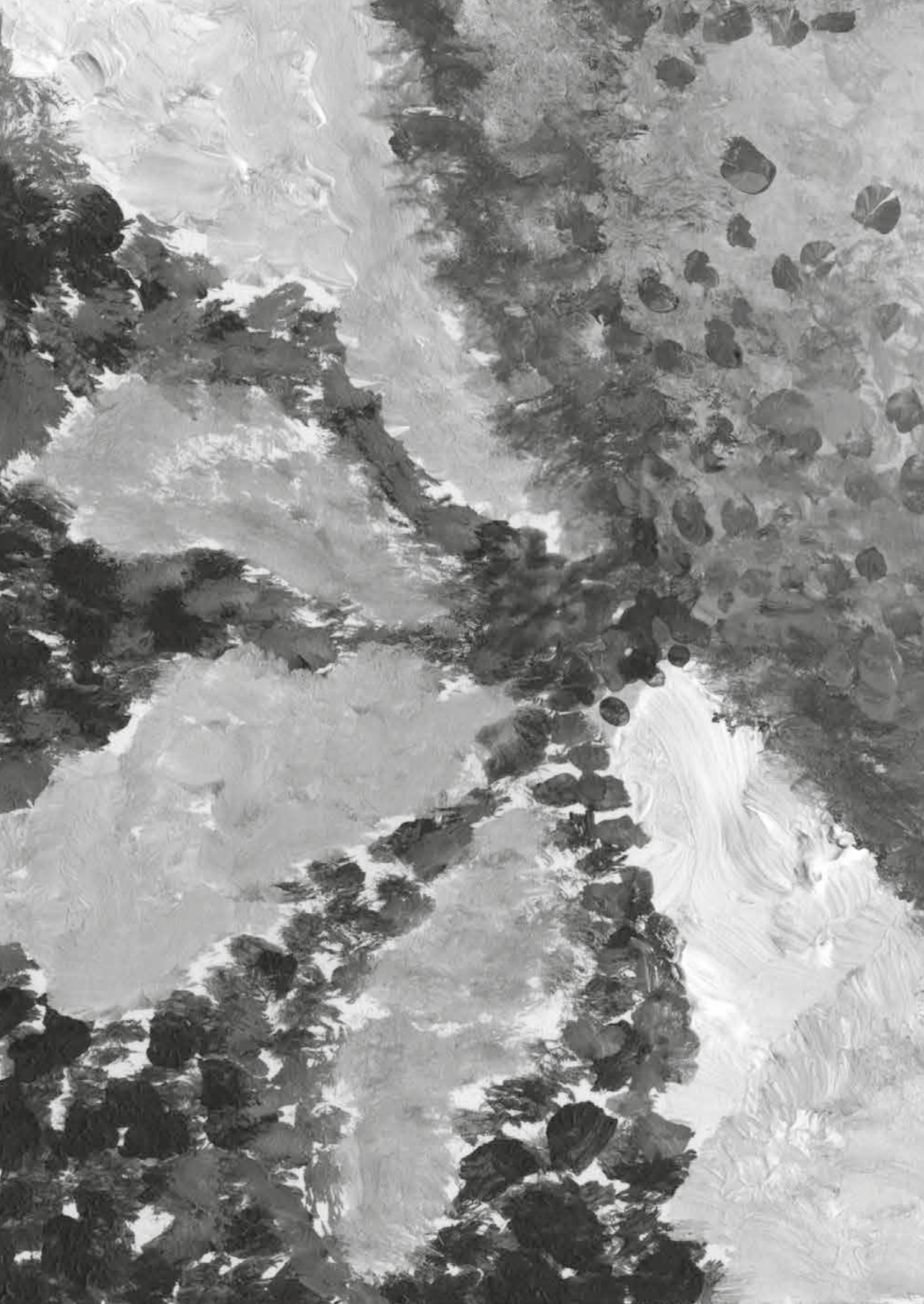
	Univariate Model*			Multivariate Model**			Backward Model*		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
<i>Sociodemographic variables</i>									
Sex (Women)				1.35	(0.88 - 2.08)	0.17	1.30	(0.87 - 1.95)	0.20
Age				1.10	(1.08 - 1.13)	0.00	1.11	(1.09 - 1.13)	0.00
Socioeconomic status	0.79	(0.57 - 1.09)	0.15	0.84	(0.60 - 1.17)	0.31			
<i>Clinical variables</i>									
ESR	1.02	(1.01 - 1.02)	0.00	1.02	(1.01 - 1.03)	0.00	1.02	(1.01 - 1.02)	0.00
DAS28	1.12	(0.94 - 1.32)	0.22	0.89	(0.72 - 1.11)	0.31			
Disease duration	1.11	(1.10 - 1.12)	0.00	1.00	(0.98 - 1.01)	0.61			
Rheumatoid factor	1.38	(0.94 - 2.02)	0.11	1.38	(0.82 - 1.83)	0.32			
Pain (VAS)	1.00	(1.00 - 1.01)	0.20	1.00	(0.99 - 1.01)	0.62			
Cardiovascular comorbidity	2.10	(1.25 - 3.52)	0.01	2.10	(1.05 - 3.15)	0.03	2.04	(1.21 - 3.43)	0.01
Hypertension	1.46	(0.99 - 2.16)	0.06	1.46	(0.87 - 3.10)	0.13			
Diabetes Mellitus	1.87	(1.04 - 3.36)	0.04	1.87	(0.89 - 2.01)	0.16	1.77	(0.97 - 3.24)	0.06
<i>Functional variables</i>									
HAQ	1.34	(1.01 - 1.78)	0.05	1.34	(0.59 - 1.51)	0.81			
SF-36, PCS	0.98	(0.97 - 1.00)	0.05	0.98	(0.96 - 1.01)	0.31			
SF-36, MCS	0.99	(0.98 - 1.01)	0.52	0.99	(0.98 - 1.01)	0.59			

Outcome Cox Regression analyses (n=882). *Adjusted for age and sex. **Adjusted for all other variables. HR = Hazard Ratio, CI = Confidence Interval, SD = Standard deviation, ESR = erythrocyte sedimentation rate, DAS28 = disease activity in 28 joints, VAS = visual analogue scale, HAQ = health assessment questionnaire, SF-36 = 36-item short form health survey, PCS = physical component summary, MCS = mental component summary.

Reference List

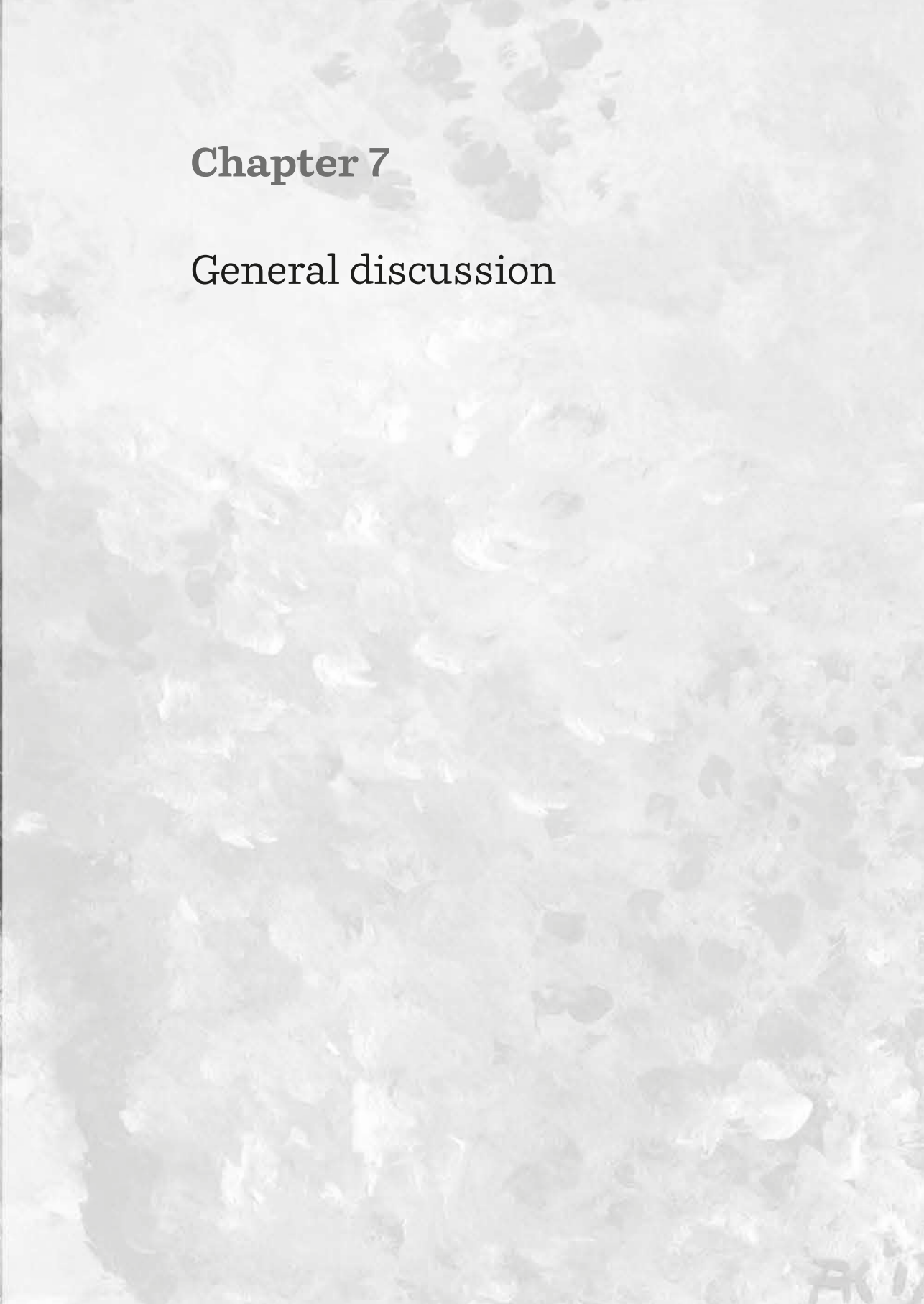
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Chapter 7

General discussion



GENERAL DISCUSSION

The aim of this thesis was to provide more insight into the long-term impact of Rheumatoid Arthritis (RA) and comorbidity on functioning and mortality. This thesis is based on a longitudinal study, the RA+ study, which started in 1997 and was originally designed to study health care and health outcomes in patients with RA.

Main findings

In this thesis we addressed five research themes. Below the main findings will be summarized successively.

1. The long-term physical functioning in patients with RA and its association with somatic comorbidity and comorbid depression (chapter 2):
We found that physical functioning improved slightly over 11 years in the total group of patients with RA. Somatic comorbidity and comorbid depression at baseline were associated with worse physical functioning over the entire 11-year followup period. Patients with RA and comorbid depression had the lowest level of physical functioning. Moreover, the presence of both somatic comorbidity and comorbid depression was associated with less improvement of physical functioning over time.
2. The impact of a wide range of specific somatic comorbidities and comorbid depression on long-term physical and mental functioning in patients with RA (chapter 3):
We found comorbid circulatory conditions, respiratory conditions, musculoskeletal conditions, cancer, and depression to be associated with worse physical functioning. Respiratory conditions and depression were associated with worse mental functioning.
3. The all-cause mortality, the trend in this mortality, and cause-specific mortality of patients with RA in comparison with the general population (chapter 4):
The observed mortality among patients with RA was 54% higher than in the general population after adjustment for age, sex, and calendar year. More than one life-year was lost over 15 years. Mortality tended to decrease over time. Mortality was higher for circulatory, respiratory, musculoskeletal and digestive system diseases.

4. The impact of somatic comorbidity and comorbid depression on mortality in patients with RA (chapter 5):
We found comorbid circulatory conditions, respiratory conditions, cancer, and depression to be associated with all-cause mortality during a 14-year followup period.
5. The cardiovascular (CV) mortality of patients with RA in comparison with the general population and the impact of a broad range of predictors (chapter 6):
CV mortality among patients with RA during the 15-year followup period was still higher than in the general Dutch population. The decrease in CV mortality in comparison with the general Dutch population was not statistically significant. Predictors for CV mortality were higher-age, higher erythrocyte sedimentation rate, CV comorbidity and diabetes mellitus.

Functioning

RA imposes a considerable burden on physical functioning. Patients with RA had, according to the SF-36, a mean physical component summary score of 37.9 during the total study period. This is much worse than the mean score of 50 in the general Dutch population (1). Moreover, the mean score for physical functioning of patients with RA was worse than physical functioning of the general older population and this difference was clinically significant (2,3). The mean physical functioning score in patients with RA was also worse in comparison with patients with other chronic diseases, such as cardiovascular diseases, respiratory diseases, diabetes and depression (4).

Our results showed that the total group of patients with RA report stable, or even a slight improvement, in physical functioning over time. We expected that physical functioning would decrease over time, given the fact that these patients had established RA and became older (5,6). However, physical functioning was stable and improved even slightly. An explanation for the improvement in physical functioning could be the introduction of tight disease control with DMARDs and the introduction of biologicals, around 2000. Another explanation might be response shift. Response shift refers to the observation that individuals tend to change the subjective evaluation of their health status as a result of changes in their objective health status (7). Response shift occurs when individuals experience changes in their health status, and as a consequence adapt their internal standards, values or conceptualization of quality of life (8).

In contrast to physical functioning, mental functioning in our cohort was comparable to the general population. This does not correspond with a recent review addressing mental functioning in patients with RA, which concluded that mental functioning in these patients was slightly lower than in the general population (9).

Longer disease duration is associated with better mental functioning (9). Our cohort comprises patients with relatively long disease duration. This might explain the relatively good mental functioning in our cohort.

Functioning and comorbidity

The presence of somatic comorbidity or comorbid depression resulted in a worse physical functioning on the long term. Patients with both somatic comorbidity and comorbid depression had the worst physical functioning. The difference between patients without comorbidity, and patients with both somatic comorbidity and comorbid depression even increased over time, resulting in a clinically relevant difference after 11 years. Especially patients with comorbid circulatory conditions, respiratory conditions, musculoskeletal conditions, cancer and depression showed worse physical functioning in the long term.

To provide both disease-specific and generic data on physical functioning, we used both the health assessment questionnaire (HAQ) and the physical scales of the SF-36. The HAQ is a disease-specific measure: it asks for activities that are specifically affected in patients with RA. The SF-36 is a generic measure, meaning that functioning is assessed in a general way – not specific to any age, disease, or treatment group (10). Our results showed that the effect of comorbid conditions is more apparent when physical functioning is measured with the SF-36. Given the high prevalence of comorbidity in patients with RA (in this cohort, more than two-thirds of the patients had ≥ 1 comorbid condition at baseline), we recommend adding the SF-36 to the HAQ to identify the full spectrum of functioning.

Mental functioning was significantly worse in patients with RA if they had a comorbid respiratory condition or depression. A study comparing mental functioning between patients with different chronic somatic diseases also showed that patients with respiratory conditions had the lowest mental functioning (11). An explanation might be that in respiratory diseases, patients experience more anxiety because of the limited exercise tolerance and dyspnea (12).

Comorbid depression

The baseline prevalence of depression in this cohort was high (28.5%) and this prevalence was more than twice as high as the prevalence of depression in the Dutch older population using the same measure (13). A recent study confirmed the high prevalence of depression in patients with RA (14). Comorbid depression occurred more often than somatic comorbidities in our cohort, which was also found in an international study addressing the prevalence of comorbidity in patients with RA (15). Various pathways may explain the link between depression and RA. Depression can

occur as a consequence of the presence of pain or loss of physical functioning, or as a consequence of RA. There is growing evidence for a link between depression and RA by inflammation (16-18). The relationship between RA and depression is partly mediated by psychological factors, such as poor coping (16, 19).

Although the prevalence of depression is high in many chronic diseases, depression is often underdiagnosed. Diagnosing major depression in physically ill patients may be difficult because 1) symptoms of depression overlap with symptoms of the physical disorder; 2) the physical disorder itself may cause depression; and 3) some degree of sadness, disappointment, and fear is normal and appropriate to the situation. Insufficient diagnostics and treatment of depression in patients with RA and chronic diseases may be related to a misconception that depressive symptoms are part of the disease and do not represent a treatable disorder (16,20).

Although it seems reasonable to recommend routine screening for and treatment of depression, evidence for the effects of routine screening on recognition rates of depression, management of depression and outcomes with respect to depression is lacking (21) also in patients with RA (22). It seems that psychological interventions (23) and exercise (24) are effective in improving physical activity and reducing depressive symptoms in patients with RA. However, the effect sizes found in these studies are small and more evidence is needed. Moreover, patients with major depression are often excluded in these studies and more research is needed to study the effectiveness of these interventions in patients with RA and comorbid depression (25). Evidence for the treatment of depression in patients with RA with antidepressants is still inconclusive (26,27).

Comorbid depression in our studies was measured with a self-reported questionnaire. Studies investigating prevalence of depression in RA populations showed that the prevalence of depression is higher if measured with self-reported measurement instruments than when diagnosed by psychiatric interview (14). The depression measured by self-report should therefore be interpreted as a possible depression (28).

All-cause, cause-specific and CV mortality

In the past years, the number of studies about the impact of RA on mortality is rising (29-35). It is expected that the intensive treatment of RA with DMARDs and biologicals would result in better disease management. Moreover, it is expected that better disease management will also result in a decrease of CV events by lowering the process of atherosclerosis. During the course of our study, treatment for patients with RA changed. From the 1990s high dose treatment with DMARDs started and biologicals were applied from 2001 onwards (36). Moreover, the management of traditional CV risk factors have been introduced (37). We expected therefore a decrease in the all-cause and CV mortality rate (38).

The results of this study showed that most often patients died due to CV diseases. CV diseases appeared to be the primary cause of death in 32% of the cases. This percentage seems to be somewhat lower than reported in older studies, conducted before implementation of intensive treatment and tight control of disease, where about 40% of the patients with RA died due to CV diseases (39). Our lower CV death rate might be related to currently applied disease management. Nevertheless, all-cause and CV mortality is still significantly higher than in the general population.

Although the all-cause and CV mortality tended to decrease over time, the decrease was not statistically significant. An explanation might be that in our cohort not all patients were treated with high dose DMARDs or biologicals from disease onset. This was a cohort of patients with established RA, and the CV related burden might have occurred in the early phases of the disease already. Thus, the effect of intensive treatment on CV mortality may be more outspoken if intensive treatment was started directly from disease onset. Our results are in accordance with other studies that also found elevated levels of mortality (30-33). Some studies, however found that mortality in patients with RA was comparable to the general population (34,40,41). Studies investigating trends in mortality and comparing cohorts of patients diagnosed before 2000 and after 2000 found inconsistent results. These inconsistent results might be the result of different types of cohort and differences in followup time (42). Studies are required investigating cohorts from disease onset and following patients during a long follow-up period. One recent study compared two cohorts, one cohort with patients diagnosed before 2006 and a cohort with patients diagnosed after 2006, after 7 years followup (43). This study found that the mortality in the second cohort was still higher than in the general population, but tended to decrease over time. So it seems that the mortality risk in comparison with the general population is still higher, but there might be a decrease in recent times.

Comorbidity and mortality

Somatic comorbidity is described in literature as one of the most important predictors for mortality in patients with RA. Comorbidity is usually measured with a dichotomous score, a sum score or an index score. For clinical practice recording specific comorbidities provides more targeted information for effective treatment. Our results showed that circulatory conditions, respiratory conditions, cancer and depression were associated with mortality. Mark that these comorbid conditions have a negative impact both on physical functioning and mortality. A further noteworthy finding was the association of depression with mortality. A study of Ang and co-workers confirmed our results (44). They found comorbid depression to be an independent risk factor for mortality in RA. Little is known about the mechanisms that account for the association between comorbid depression and mortality. Depression may increase the risk of mortality

through behavioral factors, like inactivity, smoking, poor adherence to treatment and less seeking of health care. These factors may directly or indirectly, lead to mortality (45). Depression can also increase the risk by biological factors, like dysregulation of the neuro-immune system and hyperactivity of the hypothalamic pituitary adrenal, axis (46). However this relationship is complex.

It is remarkable in our results that only 6% had a comorbid CV disease at baseline, while 32% died due to CV diseases. It is possible that the use of questionnaires at baseline to diagnose CV disease resulted in under-diagnosis. Another possible explanation for the discrepancy between CV comorbidity and CV mortality is that patients with RA have more often unrecognized coronary heart diseases and experience more often sudden death from cardiovascular causes than patients without RA (47).

Methodological considerations

The strengths of our study are its longitudinal design, its long-term followup period, the large patient sample, and the relatively high response rates during the followup period. Moreover, a wide spectrum of somatic comorbid conditions and comorbid depression was examined, and both physical and mental functioning was investigated. In addition, mortality data could be obtained for almost all patients and the high number of deaths made it possible to study the cause specific SMRs for a wide range of causes of death.

Loss to followup might introduce bias into longitudinal studies. We used a statistical model that took into account the selection bias that may have occurred (chapters 2 and 3). We optimized the estimation of physical and mental functioning by adding all baseline demographic variables that are regarded as prognostic factors for health outcomes. The model assumes that non-responders have the same physical and mental functioning during followup as comparable responders, i.e., responders with equal values for all variables in the model. Although this reduces the risk of selection bias, there is still a risk of an incorrect estimation, e.g., if non-responders have the same baseline scores as comparable responders, but the course of their physical functioning develops differently. Therefore, although this method is appropriate in addressing selection bias (48), there still remains a risk of bias due to loss to followup.

Somatic comorbidity was measured with a self-report list abstracted from the Health Interview Survey of Statistics Netherlands (49). Self-reporting may have led to underestimation. However, the list that was used has been tested for its validity in a separate study, whereby patients' self-reported data were compared with general practitioners' (GP) reported data derived from the medical record. The results of this validation study indicated that the agreement between patient self-reported and GP reported was high (50). Comorbid depression was also measured with a self-reported questionnaire. As stated above, studies investigating prevalence of depression in RA populations showed that the prevalence of depression is higher if measured with self-

reported measurement instruments than when diagnosed by psychiatric interview (14). The depression measured by self-report should therefore be interpreted as a possible depression (28).

We observed a trend towards a decrease in mortality (chapter 4). One explanation for the decreasing mortality might be that our cohort was a fixed cohort, hence new patients could not enter the study. As a result the improved mortality could be a survival effect, in which patients with more "severe" RA died at the start of the study period (for example patients with shorter disease duration or with rheumatoid factor positive) and less "severe" patients survived and were followed up to the end of the study, which resulted in lower Standardized Mortality Ratio at the end of the study period.

This study was initially designed to study health care and health outcomes in patients with RA. The RA+ study, focused on a limited set of background variables, which hampers more detailed analyses. So we did not have data about important potential confounders of CV mortality, such as smoking, BMI and cholesterol (chapter 6). We found that musculoskeletal and connective tissue diseases were the primary cause of a high number of deaths (chapter 4). This does not correspond with other studies, which report that RA is the primary cause of death in only a few cases (51). This might be due to the definition used by Statistics Netherlands. In their databank the primary cause of death is defined as the underlying cause of death, or the disease that started a sequence of incidents that resulted in death (52). Different definitions of cause of death, used in national registries, will have important implications for study results. Therefore, results addressing cause-specific mortality, originating from different national registries, should be interpreted with caution.

Clinical relevance

Our results stress the importance of paying attention to comorbid conditions in clinical practice. Patients with RA and comorbidity, in particular patients with circulatory, respiratory, musculoskeletal conditions, cancer, and comorbid depression remain behind in physical functioning over 11 years of followup. Patients with circulatory, respiratory conditions, cancer and depression also have a higher mortality risk. As such, it is important to ascertain the presence of such comorbidities at an early stage so that treatment can be adjusted accordingly. A recent study found that the detection and management of comorbidities in RA is far from optimal (15). Raising awareness among rheumatologist about the importance of comorbidity in patients with RA could contribute to increasing the quality of care for and, in the end, the quality of life of these patients.

How to implement such a recommendation in daily clinical practice will depend on the structure of the health care system at hand. In the Netherlands, this recommendation could necessitate an important role for rheumatologists and general practitioners in

monitoring, referring, and coordinating care. In addition, intervention strategies should be developed for the adequate treatment and management of somatic comorbidity and comorbid depression to reduce their negative impact on physical functioning and to improve clinical outcomes. This requires integration of care of different professions. Health care should aim at optimizing outcomes for patients and should be organized around the care path of patients and not around medical specialties (53). Alongside pharmacologic treatment, aiming at reducing disease activity, multidisciplinary rehabilitation could further improve physical and mental functioning through nonpharmacologic treatment modalities (54). Assessing comorbidity and adequate disease management for comorbidity are crucial parts of the clinical evaluation and treatment of patients with RA (55).

In patients with established RA the mortality risk is still higher than mortality in the general Dutch population, with more than a life-year lost over a period of 15 years. As the primary cause of death is mostly CV, disease screening for and providing information about CV diseases (and CV risk factors) in rheumatology practice is important. On the other hand the decrease in mortality coincided with changes in medication policy. Hence, tight disease control seems also important to lower the high mortality risk in RA. As CV mortality in RA is still higher than in the general population, continued attention for CV diseases in RA is important. Both tight control of disease activity and good care for comorbid conditions (CV diseases and DM) are strongly advocated.

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Chapter &

Summary

Nederlandse samenvatting

List of publications

Contributing authors

Author contributions

About the author

Dankwoord

SUMMARY

The long-term impact of rheumatoid arthritis and comorbidity on functioning and mortality

This thesis presents the results of a longitudinal study on comorbidity, functioning and mortality in patients with rheumatoid arthritis (RA).

RA is a chronic, systemic, inflammatory autoimmune disease characterized by pain and swelling of multiple joints of the body. Extra articular and systemic manifestations are also part of the disease. RA is associated with emerging comorbidities resulting in substantial impacts on functioning and mortality. Limited information exists on these interrelationships.

Comorbidity, defined as any additional, coexistent condition in a patient with a particular index disease, is highly prevalent in patients with RA. Many patients with RA suffer from somatic comorbidities as well as psychological comorbidity, particularly depression. Both physical functioning and mental functioning are important outcomes in patients with RA. Several studies have reported the negative association between comorbidity and functioning in the short term (<5 years). Little is known about the impact of comorbidity in the longer term, which is particularly relevant for chronic diseases with a course of slow decline. Moreover, little is known about the effects of a wide range of specific comorbid conditions on physical and mental functioning. More knowledge on these associations will help clinicians to estimate the prognosis of individual patients with specific comorbidities and to determine treatment options.

Patients with RA have a higher mortality risk in comparison with the general population. The higher mortality rate in patients with RA is mainly attributable to cardiovascular (CV) diseases. In the past decades treatment of RA improved substantially and this might impact on the risk of mortality in patients with RA. Studies that started around 2000, after the introduction of biologicals, showed contradictory results, in analysing time trends in all-cause mortality. Some studies report that the mortality in patients with RA was similar to that of the general population, while others showed that the mortality in patients with RA was higher or that the mortality gap with the general population was even increasing. Given these conflicting results, there is a need to evaluate the risk of all-cause and CV mortality in a large sample of patients with RA, over a long period, using recent mortality data.

Comorbidity is one of the most significant predictors for mortality in patients with RA. Which specific comorbidities are associated with mortality has been less

investigated. Thus, there is also a need to study for a wide range of comorbid conditions the association with mortality in patients with RA to obtain a more comprehensive view and to provide clinically useful tools for optimizing care.

Chapter 1 provides a general introduction to the research themes of this thesis. The main concepts – comorbidity, functioning and mortality – are introduced, the study design is described and an outline of the thesis is given. This thesis aims to provide more insights into the long-term impact of RA and comorbidity on functioning (**chapter 2 and 3**) and mortality (**chapters 4-6**).

Chapter 2 describes the long-term physical functioning and its association with somatic comorbidity and comorbid depression in patients with RA (n=882). Longitudinal data over a period of 11 years were collected. Patient reported outcomes were collected in 1997, 1998, 1999, 2002, and 2008. Physical functioning was measured with the Health Assessment Questionnaire (HAQ) and the physical component summary score of the Short Form 36 (SF-36) health survey. Somatic comorbidity was measured with a list of 12 groups of chronic diseases adapted from the Health Interview Survey of Statistics Netherlands. Comorbid depression was measured with the Center for Epidemiologic Studies Depression Scale. Four groups of patients were distinguished based on the presence of comorbidity at baseline: patients without comorbidity, patients with somatic comorbidity only, patients with comorbid depression only, and patients with both somatic comorbidity and comorbid depression. At baseline, 68% of all patients had ≥ 1 comorbid condition. For the total group of patients with RA, physical functioning improved slightly over time. Somatic comorbidity and comorbid depression at baseline were associated with worse long-term physical functioning over the entire 11 year followup period. Patients with RA and comorbid depression had the lowest level of physical functioning. Moreover, the presence of both somatic comorbidity and comorbid depression was associated with less improvement of physical functioning over time. These results emphasize the need for paying attention to both somatic comorbidity and comorbid depression in clinical practice.

In **chapter 3** the results of a longitudinal study with 11 years of followup are presented. The impact of a wide range of specific somatic comorbidities and comorbid depression on long-term physical and mental functioning in patients with RA (n=882) was studied. Results showed that the effect of comorbid conditions was more apparent when physical functioning was measured with SF-36, a disease-generic measure, compared with the HAQ, a disease-specific measure. Circulatory conditions and depression were associated with worse physical functioning according to the HAQ. Respiratory conditions, musculoskeletal conditions, cancer, and depression were associated with worse physical functioning according to the SF-36. Respiratory conditions and depression were associated with worse mental functioning. Targeted attention for these specific comorbid conditions by clinicians is recommended.

In **chapter 4**, all-cause mortality in patients with RA (n=1222) in comparison with the general population during a 15 year followup period is described. The trend in all-cause mortality ratio was investigated and the causes of death were examined and compared with the general population. The standardized mortality ratio (SMR) for all-cause mortality and the number of life years lost in the study period, adjusted for age, sex, and calendar year, were calculated. A linear Poisson regression analysis was performed to evaluate change in all-cause SMR over time. The estimated SMR (95% CI) for all-cause mortality was 1.54 (1.41, 1.67), with about one life-year lost over the study period. Results of the regression analysis showed that there was a trend to decreasing SMR (2% annually, $p=.07$) over time. Mortality in comparison with the general population was higher for circulatory, respiratory, musculoskeletal and digestive system diseases.

Chapter 5 examines the impact of a wide range of comorbid conditions on all-cause mortality in a longitudinal study with 14 years of followup. Longitudinal data were collected from 882 patients with RA. Cox regression was used to study the relationship between comorbidity and mortality. A total of 345 patients died during the study period. Comorbidities that were associated with all-cause mortality were circulatory conditions (hazard ratio [HR] 1.60 [95% CI 1.15, 2.22]), respiratory conditions (HR 1.43 [95% CI 1.09, 1.89]), cancer (HR 2.00 [95% CI 1.28, 3.12]), and depression (HR 1.35 [95% CI 1.06, 1.72]). Careful monitoring of these comorbidities during the course of the disease and adequate referral may improve health outcomes and chances of surviving.

Chapter 6 describes the CV mortality in patients with RA (n = 1222) in comparison with the general population during a 15-year followup period. The aims were to study the trend in CV mortality and the impact of a broad range of variables on CV mortality. The SMR for CV mortality was calculated. A linear Poisson regression analysis was performed to investigate if there was a trend in SMR over time. A Cox regression analysis was performed to determine which baseline variables predicted CV mortality. Estimated SMR (95% CI) for CV mortality was 1.24 (1.05, 1.43). The SMR decreased with 3% annually ($p = .16$). Predictors for CV mortality were higher age, higher erythrocyte sedimentation rate, CV comorbidity and diabetes mellitus (DM). As CV mortality in RA is still higher than in the general population, continued attention for CV diseases in RA is important. Both tight control of disease activity and good care for comorbid conditions (CV diseases and DM) are advocated.

Finally, in **chapter 7** the main results of this thesis are summarized and discussed and implications for future research and clinical practice are given.

SAMENVATTING

De lange termijn impact van reumatoïde artritis en comorbiditeit op functioneren en sterfte

Dit proefschrift geeft de resultaten weervan een longitudinale studie naar comorbiditeit, functioneren en sterfte bij patiënten met reumatoïde artritis (RA). RA is een chronische, systemische, inflammatoire auto-immuunziekte die wordt gekenmerkt door pijn en zwelling van meerdere gewrichten in het lichaam. Extra-articulaire en systemische verschijnselen zijn tevens onderdeel van de ziekte. RA gaat niet zelden gepaard met bijkomende – somatische of psychische - aandoeningen (comorbiditeit) met vaak grote gevolgen voor het functioneren en de sterfte van RA patiënten.

RA laat zowel het fysiek als het mentaal functioneren niet ongemoeid. Diverse studies hebben een negatieve associatie tussen comorbiditeit en functioneren op korte termijn (<5 jaar) aangetoond. Er is echter weinig bekend over de gevolgen van comorbiditeit op lange termijn. Een lange tijdshorizon is van belang, omdat het beloop van chronische ziekten vaak een langzame progressie laat zien. Daarnaast is er weinig bekend over de effecten van verschillende specifieke aandoeningen op het fysiek en mentaal functioneren. Indien er meer bekend is over deze relaties, kan dit klinici helpen om de prognose van een individuele RA patiënt met een specifieke bijkomende aandoening beter in te schatten en de behandeling hierop aan te passen.

RA patiënten hebben een groter sterfterisico dan de algemene populatie. Het risico om voortijdig te overlijden wordt vooral veroorzaakt door cardiovasculaire (CV) aandoeningen. In de afgelopen decennia heeft de behandeling van RA patiënten grote veranderingen doorgemaakt, wat mogelijk invloed heeft op het sterfterisico van RA patiënten. Studies die zijn gestart na de komst van biologicals, rond het jaar 2000, lieten tegenstrijdige resultaten zien wat betreft de trend in sterfte over de tijd. Een aantal studies vond dat het sterfterisico bij RA patiënten gelijk was aan dat van de algemene bevolking. Terwijl andere studies lieten zien dat de kans om voortijdig te overlijden bij RA patiënten juist groter was of zelfs was toegenomen in vergelijking met de algemene bevolking. Vanwege deze tegenstrijdige resultaten is het van belang om in een groot cohort van RA patiënten over een lange, recente periode de sterfte in het algemeen (ongeacht de doodsoorzaak) en de sterfte aan CV aandoeningen te onderzoeken.

Comorbiditeit is een van de belangrijkste voorspellers van sterfte bij RA patiënten. Comorbiditeit wordt over het algemeen gemeten met een somscore of een indexscore.

Welke specifieke comorbiditeiten geassocieerd zijn met sterfte is veel minder vaak onderzocht. Het is daarom aangewezen om voor een groot aantal specifieke comorbiditeiten de samenhang met sterfte bij RA patiënten te onderzoeken.

Hoofdstuk 1 geeft een algemene introductie van de onderzoeksthema's van dit proefschrift. De belangrijkste concepten – comorbiditeit, functioneren en sterfte – worden besproken, het studiedesign wordt beschreven en de opzet van het proefschrift wordt toegelicht. Het doel van dit proefschrift is het bestuderen van de impact van RA en comorbiditeit op functioneren (**hoofdstuk 2 en 3**) en sterfte (**hoofdstukken 4-6**).

Hoofdstuk 2 beschrijft het fysiek functioneren op lange termijn en de associatie met somatische comorbiditeit en comorbide depressie bij RA patiënten (n=882). Longitudinale data werden verzameld over een periode van 11 jaar, waarbij vragenlijsten werden afgenomen in 1997, 1998, 1999, 2002 en 2008. Fysiek functioneren werd gemeten met de Health Assessment Questionnaire (HAQ) en de fysieke component van de Short Form 36 (SF-36) health survey. Somatische comorbiditeit werd vastgesteld op basis van zelfrapportage met een lijst van 12 chronische aandoeningen. Deze lijst werd samengesteld aan de hand van de gezondheidsenquête van het Centraal Bureau voor de Statistiek. Comorbide depressie werd gemeten met de Center for Epidemiologic Studies Depression Scale. Vier groepen patiënten werden onderscheiden, op basis van de aanwezige comorbiditeit bij de start van de studie: patiënten zonder comorbiditeit, patiënten met alleen een comorbide somatische aandoening, patiënten met alleen comorbide depressie en patiënten met zowel een comorbide somatische aandoening als comorbide depressie. Bij de start van de studie had 68% van de patiënten ≥ 1 comorbide aandoening. Voor de totale groep RA patiënten verbeterde het fysiek functioneren over de tijd in lichte mate. Somatische comorbiditeit en comorbide depressie hingen samen met een slechter fysiek functioneren over de gehele periode van 11 jaar. RA patiënten met comorbide depressie hadden het slechtste fysiek functioneren. Daarnaast was de combinatie van somatische comorbiditeit en comorbide depressie geassocieerd met een verminderde vooruitgang van fysiek functioneren over de periode van 11 jaar. Gezien deze resultaten is het van belang systematisch aandacht te besteden aan somatische comorbiditeit en comorbide depressie in de klinische praktijk.

In **hoofdstuk 3** worden de resultaten van een longitudinale studie met een follow-up van 11 jaar beschreven. Onderzocht werd de impact van een groot aantal specifieke somatische aandoeningen en comorbide depressie op fysiek en mentaal functioneren bij RA patiënten (n=882). De resultaten lieten zien dat het effect van comorbiditeit op fysiek functioneren beter kon worden aangetoond met de SF-36, een generieke vragenlijst, dan met de HAQ, een ziekte-specifieke vragenlijst. CV aandoeningen en depressie waren geassocieerd met een slechter fysiek functioneren gemeten met de HAQ. Respiratoire aandoeningen, aandoeningen van het bewegingsapparaat, kanker en depressie waren geassocieerd met een slechter fysiek functioneren gemeten met de SF-36.

Respiratoire aandoeningen en depressie waren geassocieerd met een slechter mentaal functioneren.

In **hoofdstuk 4** is de sterfte in het algemeen beschreven in een cohort van RA patiënten (n=1222) vergeleken met de algemene bevolking gedurende een periode van 15 jaar. Onderzocht werd de trend in sterfte en daarnaast werden de achterliggende doodsoorzaken bestudeerd en vergeleken met die van de algemene bevolking. Berekend werden de gestandaardiseerde mortaliteitsratio (SMR) voor de sterfte in het algemeen en het aantal jaren afgenomen levensverwachting gedurende de studieperiode, gecorrigeerd voor leeftijd, geslacht en kalenderjaar. Om het beloop in SMR over de tijd te berekenen werd een lineaire Poisson regressie analyse uitgevoerd. De geschatte SMR (95% CI) voor de sterfte in het algemeen was 1,54 (1,41, 1,67), met een afgenomen levensverwachting van ongeveer 1 jaar gedurende de studieperiode. Resultaten van de regressieanalyse lieten zien dat er sprake was van een trend in afname van de SMR (2% jaarlijks, $p=0,07$). De sterfte in vergelijking met de algemene bevolking was hoger voor CV aandoeningen, respiratoire aandoeningen, aandoeningen van het bewegingsapparaat en aandoeningen van het spijsverteringsstelsel.

Hoofdstuk 5 beschrijft de impact van een groot aantal comorbide aandoeningen op de sterfte in het algemeen, onderzocht in een longitudinale studie met een follow-up van 14 jaar. Data werden verzameld van 882 RA patiënten. De relatie tussen comorbiditeit en mortaliteit werd onderzocht door middel van een Cox regressie analyse. Tijdens de studieperiode stierven in totaal 345 patiënten. Comorbide aandoeningen die samenhangen met de sterfte, waren CV aandoeningen (hazard ratio [HR] 1,60 [95% CI 1,15, 2,22]), respiratoire aandoeningen (HR 1,43 [95% CI 1,09, 1,89]), kanker (HR 2,00 [95% CI 1,28, 3,12]) en depressie (HR 1,35 [95% CI 1,06, 1,72]). Zorgvuldige monitoring van deze comorbiditeiten gedurende het beloop van de ziekte en adequate verwijzing kunnen mogelijk de gezondheidsuitkomsten en overlevingskansen van RA patiënten verbeteren.

Hoofdstuk 6 beschrijft de sterfte aan CV aandoeningen bij RA patiënten (n=1222) in vergelijking met de algemene bevolking gedurende een periode van 15 jaar. Onderzocht werd de trend in sterfte aan CV aandoeningen en daarnaast werd de impact op sterfte aan CV aandoeningen voor een groot aantal variabelen bestudeerd. De SMR voor sterfte aan CV aandoeningen werd berekend en een lineaire Poisson regressie analyse werd uitgevoerd om te onderzoeken of de SMR gedurende de studieperiode veranderde. Een Cox regressie analyse werd uitgevoerd om te bepalen welke variabelen sterfte aan CV aandoeningen voorspellen. De geschatte SMR (95% CI) voor sterfte aan CV aandoeningen was 1,24 (1,05, 1,43). De SMR nam met 3% per jaar af ($p=0,16$). Voorspellers voor sterfte aan CV aandoeningen waren hogere leeftijd, hogere bloedbezinkingssnelheid, CV comorbiditeit en diabetes mellitus (DM). Omdat de sterfte aan CV aandoeningen nog steeds hoger is bij RA patiënten dan in de algemene bevolking, is het belangrijk dat er gericht aandacht is voor CV aandoeningen. Zowel het onder controle houden van de ziekteactiviteit als goede zorg voor comorbiditeiten (CV aandoeningen en DM) wordt aanbevolen.

Tot slot zijn in **hoofdstuk 7** de belangrijkste resultaten van dit proefschrift samengevat en bediscussieerd en zijn implicaties voor toekomstig onderzoek en de klinische praktijk besproken.

LIST OF PUBLICATIONS

van den Hoek J, Roorda LD, Boshuizen HC, van Hees J, Rupp I, Tijhuis GJ, Dekker J, van den Bos GAM. Long-term physical functioning and its association with somatic comorbidity and comorbid depression in patients with established rheumatoid arthritis: a longitudinal study. *Arthritis Care and Research (Hoboken)* 2013; 65: 1157-65.

Peter WF, Loos M, **van den Hoek J**, Terwee CB. Validation of the Animated Activity Questionnaire (AAQ) for patients with hip and knee osteoarthritis: comparison to home-recorded videos. *Rheumatology International* 2015; 35: 1399-408.

van den Hoek J, Roorda LD, Boshuizen HC, Tijhuis GJ, van den Bos GAM, Dekker J. Physical and mental functioning in patients with established rheumatoid arthritis over an 11-year followup period: the role of specific comorbidities. *The Journal of Rheumatology* 2016; 43: 307-14.

van den Hoek J, Boshuizen HC, Roorda LD, Tijhuis GJ, Nurmohamed MT, Dekker J, van den Bos GAM. Association of somatic comorbidities and comorbid depression with mortality in patients with rheumatoid arthritis: a 14-year prospective cohort study. *Arthritis Care and Research (Hoboken)* 2016; 68: 1055-60.

van den Hoek J, Roorda LD, Boshuizen HC, Tijhuis GJ, Dekker J, van den Bos GAM, Nurmohamed MT. Trend in and predictors for cardiovascular mortality in patients with rheumatoid arthritis over a period of 15 years: a prospective cohort study. *Clinical and Experimental Rheumatology* 2016; 34: 813-19

van den Hoek J, Boshuizen HC, Roorda LD, Tijhuis GJ, Nurmohamed MT, van den Bos GAM, Dekker J. Mortality in patients with rheumatoid arthritis: a 15-year prospective cohort study. *Rheumatology International* 2017; 37: 487-493.

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AUTHOR CONTRIBUTIONS

Chapter 2

Long-term physical functioning and its association with somatic comorbidity and comorbid depression in patients with established rheumatoid arthritis: a longitudinal study.

J van den Hoek, LD Roorda, HC Boshuizen, J van Hees, I Rupp, GJ Tijhuis, J Dekker, GAM van den Bos

Study conception and design: Van den Bos, Boshuizen, Roorda, Rupp. Acquisition of data: Rupp, Van Hees. Analysis and interpretation of data: Van den Hoek, Van den Bos, Dekker, Roorda, Boshuizen, Tijhuis. All authors were involved in drafting the article and contributed to critical revision of the manuscript. All authors approved the final version to be published.

Chapter 3

Physical and mental functioning in patients with established rheumatoid arthritis over an 11-year followup period: the role of specific comorbidities.

J van den Hoek, LD Roorda, HC Boshuizen, GJ Tijhuis, GAM van den Bos, J Dekker

Study conception and design: van den Bos, Dekker, Roorda, Boshuizen. Acquisition of data: Rupp, Van Hees. Analysis and interpretation of data: Van den Hoek, Dekker, Van den Bos, Roorda, Boshuizen, Tijhuis. All authors were involved in drafting the article and contributed to critical revision of the manuscript. All authors approved the final version to be published.

Chapter 4

Mortality in patients with rheumatoid arthritis: a 15-year prospective cohort study.

J van den Hoek, HC Boshuizen, LD Roorda, GJ Tijhuis, MT Nurmohamed, GAM van den Bos, J Dekker

Study conception and design: Van den Bos, Dekker, Van den Hoek, Boshuizen, Roorda. Acquisition of data: Van den Hoek. Analysis and interpretation of data: Van den Hoek, Boshuizen, Dekker, Van den Bos, Roorda, Nurmohamed, Tijhuis. All authors were involved in drafting the article and contributed to critical revision of the manuscript. All authors approved the final version to be published.

Chapter 5

Association of somatic comorbidities and comorbid depression with mortality in patients with rheumatoid arthritis: a 14-year prospective cohort study.

J van den Hoek, HC Boshuizen, LD Roorda, GJ Tijhuis, MT Nurmohamed, J Dekker, GAM van den Bos

Study conception and design: Van den Hoek, Van den Bos, Dekker, Boshuizen, Roorda. Acquisition of data: Van den Hoek. Analysis and interpretation of data: Van den Hoek, Van den Bos, Dekker, Boshuizen, Roorda, Nurmohamed, Tijhuis. All authors were involved in drafting the article and contributed to critical revision of the manuscript. All authors approved the final version to be published.

Chapter 6

Trend in and predictors for cardiovascular mortality in patients with rheumatoid arthritis over a period of 15 years: a prospective cohort study.

J van den Hoek, LD Roorda, HC Boshuizen, GJ Tijhuis, J Dekker, GAM van den Bos, MT Nurmohamed

Study conception and design: Van den Hoek, Van den Bos, Dekker, Roorda, Boshuizen, Nurmohamed. Acquisition of data: Van den Hoek. Analysis and interpretation of data: Van den Hoek, Boshuizen, Nurmohamed, Van den Bos, Dekker, Roorda, Tijhuis. All authors were involved in drafting the article and contributed to critical revision of the manuscript. All authors approved the final version to be published.

ABOUT THE AUTHOR*Curriculum vitae**PhD Portfolio*

CURRICULUM VITAE

Joëlle van den Hoek was born on November 14, 1983 in Apeldoorn, The Netherlands. She completed her pre-university secondary education at the Baudartius College in Zutphen and studied physical therapy at the Hanzehogeschool Groningen from 2002 to 2006. After graduation, she followed the pre-master and master Human Movement Sciences at the Rijksuniversiteit Groningen from 2006 to 2009. Along with her study Human Movement Sciences, she worked as a physiotherapist in a primary care center. After graduation, she started working as a physiotherapist in Reade, center for rehabilitation and rheumatology in Amsterdam in 2009. In 2011 she started the PhD project at Reade and the department of Social Medicine of the Academic Medical Center in Amsterdam under supervision of prof. dr. G.A.M. van den Bos and prof. dr. J. Dekker, which resulted in this thesis. During her PhD project, she worked between 24 and 34 hours a week as a physiotherapist in the multidisciplinary treatment of patients with rheumatic diseases at Reade. She completed her PhD project in 2017. Joëlle lives together with her husband and son in Amsterdam.



PhD PORTFOLIO

Joëlle van den Hoek

PhD period: 2011 – 2017

PhD supervisors: prof. dr. G.A.M. van den Bos and prof. dr. J. Dekker

	Year	Workload (ECTS)
General courses		
Good clinical practice, in company course, Reade	2011	1.0
English writing, in company course, Reade	2012	0.4
Specific courses		
Regression analysis, Leids Universitair Medisch Centrum	2012	1.5
Clinical epidemiology, Graduate School AMC	2013	0.6
Advanced topics in Clinical Epidemiology, Graduate School AMC	2013	1.1
Presentations		
Annual congress Nederlandse Vereniging voor Reumatologie, Arnhem, The Netherlands. Poster presentation.	2011	0.5
Meeting doctors in Rehabilitation, Amsterdam, The Netherlands. Oral presentation.	2011	0.5
Annual congress European League Against Rheumatism, Berlin Germany. Two poster presentations.	2012	1.0
Annual congress European League Against Rheumatism, Paris, France. Two poster presentations	2014	1.0
ACR/ARHP annual meeting. American College of Rheumatology congress, Boston, USA. Two poster presentations.	2014	1.0
Annual congress Nederlandse Vereniging voor Reumatologie, Arnhem, The Netherlands. Two oral presentations and poster presentation.	2014	1.5
Annual congress European League Against Rheumatism, Rome, Italy. Poster presentation.	2015	0.5
Annual congress Nederlandse Vereniging voor Reumatologie, Arnhem, The Netherlands. Oral presentation and poster presentation.	2015	1.0
Jaarcongres Koninklijk Nederlands Genootschap voor Fysiotherapie, Utrecht, The Netherlands. Two poster presentations.	2016	1.0
(Inter)national conferences		
Annual congress European League Against Rheumatism, London, United Kingdom.	2011	0.75
Annual congress Nederlandse Vereniging voor Reumatologie, Arnhem, The Netherlands.	2011	0.25
World Congress Physical Therapy, Amsterdam, The Netherlands.	2011	0.25
Annual congress European League Against Rheumatism, Berlin, Germany.	2012	0.75
Annual congress European League Against Rheumatism, Madrid, Spain.	2013	0.5
Annual congress European League Against Rheumatism, Paris, France.	2014	0.75
ACR/ARHP annual meeting. American College of Rheumatology, Boston, USA.	2014	1.5
Annual congress Nederlandse Vereniging voor Reumatologie, Arnhem, The Netherlands.	2014	0.5
Annual congress European League Against Rheumatism, Rome, Italy.	2015	0.75

Annual congress Nederlandse Vereniging voor Reumatologie, Arnhem, The Netherlands.	2015	0.5
Wetenschapsdag, Wetenschappelijk College Fysiotherapie, Amersfoort, The Netherlands.	2016	0.25
Jaarcongres Koninklijk Nederlands Genootschap voor Fysiotherapie, Utrecht, The Netherlands.	2016	0.25
Annual congress European League Against Rheumatism, London, United Kingdom.	2016	0.75
Other		
Meeting PhD students Reade (monthly, 1 hour)	2011-2017	2.5
Scientific meeting Reade (monthly, 1.5 hours)	2011-2015	3.0
Scientific symposia Reade (twice a year)	2011-2017	1.5
Co-author of chapter 'Diseases of the joints' in textbook for junior doctors in rehabilitation	2012	1.0
Working as a physiotherapist in a rehabilitation center for patients with Rheumatoid Arthritis (24-34 hours/week)	2009 - now	
Teaching		
Workshop guideline osteoarthritis for physical therapists	2012	0.4
Workshop physical therapy in arthritis/osteoarthritis for junior doctors in rehabilitation	2013	0.6
Grants		
Travel grant application for the EULAR Congress	2012	
Travel grant application for the EULAR Congress	2014	
Reumafonds travel grant application for the ACR/ARHP annual meeting	2014	
Travel grant application for the EULAR Congress	2015	

DANKWOORD

De afgelopen jaren waarin ik gewerkt heb aan dit proefschrift waren leerzaam en leuk. Kenmerkend voor het proces vond ik de prettige samenwerking binnen de onderzoeksgroep. Iedereen was kritisch, maar vooral betrokken en enthousiast. Dit motiveerde om steeds weer aan de slag te gaan. Via deze weg wil ik iedereen bedanken die dit proefschrift mogelijk heeft gemaakt. Een aantal personen en groepen wil ik graag uitlichten.

Dit proefschrift had nooit tot stand kunnen komen zonder de patiënten die hebben deelgenomen aan het onderzoek. Ik wil u hartelijk danken voor het invullen van de vele vragenlijsten. Velen van u zijn gedurende een periode van 11 jaar betrokken geweest bij het onderzoek en waren steeds opnieuw bereid om mee te werken. Heel erg veel dank daarvoor.

Mijn promotor, prof. dr. G.A.M. van den Bos. Beste Trudi, ontzettend bedankt voor al je hulp en steun. Je bent kritisch en legt de lat hoog, maar je bent ook positief. Je positieve feedback was steeds een enorme motivatie om weer verder aan de slag te gaan. Vooral in de laatste fase van het proefschrift hebben we veel contact gehad, ik waardeer je (persoonlijke) betrokkenheid en hartelijkheid enorm.

Mijn promotor, prof. dr. J. Dekker. Beste Joost, dank voor je scherpe blik, jij wist soms de vraagstukken van een andere kant te bekijken. Je wees me steeds op het belang het onderzoek kort en kernachtig te omschrijven. Je bent zakelijk als het gaat om zaken rondom dit proefschrift, maar ik ben blij dat ik tijdens de EULAR reizen en etentjes met de onderzoekers ook je persoonlijke kant heb mogen ervaren.

Mijn co-promotor, dr. L.D. Roorda. Beste Leo, allereerst dank dat je me betrokken hebt bij dit onderzoek. Je werkt erg gestructureerd en bracht dit ook over. Daarnaast was je altijd beschikbaar voor vragen, 's avonds, in het weekend, soms zelfs wanneer jij op vakantie was. Je was altijd positief, ook wanneer het soms tegenzat, bleef jij optimistisch en wist je de positieve punten van het onderzoeksproces te benoemen. Bedankt, ik heb veel van je geleerd.

Mijn co-promotor, prof. dr. H.C. Boshuizen. Beste Hendriek, heel erg veel dank voor je bijdrage op methodologisch en statistisch vlak. Ik heb veel van je geleerd. Ik heb veel respect voor al je kennis en de duidelijkheid waarmee je de methodologie over weet te brengen. Je bent geduldig en ik kon altijd bij je terecht.

De andere leden van de onderzoeksgroep. Prof. dr. M.T. Nurmohamed. Beste Mike, dank voor je bijdrage aan de artikelen over mortaliteit. Dank voor het delen van je kennis op het gebied van cardiovasculaire aandoeningen bij reumatoïde artritis en je klinische blik. Dr. G.J. Tijhuis. Beste Gerard, dank voor je klinische bijdrage aan de

artikelen. Dr. I. Rupp. Beste Ines, dank voor het mede opzetten van het onderzoek en het meelesen en kritisch beoordelen van het eerste artikel.

Leden van de promotiecommissie, prof. dr. V. de Groot, prof. dr. R.J. de Haan, prof. dr. F. Nollet, prof. dr. D. van Schaardenburg en prof. dr. F.G. Schellevis, dank voor het kritisch beoordelen van het manuscript.

Raad van bestuur van Reade, dank voor het mogelijk maken van dit onderzoek. Wat is het goed dat in dit centrum de mogelijkheid bestaat om (paramedische) zorg en onderzoek te combineren, zodat vragen vanuit de klinische praktijk onderzocht kunnen worden en op deze manier de revalidatiezorg steeds verder verbeterd kan worden.

Medewerkers van het Centraal Bureau voor de Statistiek, dank voor jullie hulp bij het verzamelen van de gegevens over sterfte.

Reumafonds en EULAR dank voor het verstrekken van subsidie om naar internationale congressen te kunnen gaan.

Lieve collega's van de POK, Martin, Marike, Aleid, Arjan, Jasmijn, Jesper, Joyce, Lisa, Mariëtte, Marloes, Martine, Salima en Wilfred., wat is het fijn om met jullie te werken! Jullie zitten of zaten allemaal in het zelfde traject en kennen de hoogte- en dieptepunten. Wat fijn om samen te sparren over het onderzoek, maar ook om ideeën uit te wisselen over hoe zorg en onderzoek beter kunnen. We delen de ambitie om door middel van onderzoek de fysiotherapeutische en revalidatiezorg te verbeteren. Naast inhoudelijk interessant is het ook gezellig: ik denk aan de vele internationale congressen die we hebben gehad, (soms zelfs in Boston), maar ook aan de vele etentjes. Ik ben erg blij met jullie als collega.

Beste collega's fysiotherapie en reumarevalidatie. Wat een prettige omgeving om in te werken. Door kritisch te zijn, te overleggen en te discussiëren proberen we de zorg voor de patiënten zo goed mogelijk te maken. Mede door de prettige werksfeer en jullie begrip heb ik dit onderzoek tot een goed einde kunnen brengen.

Beste Inge, dank voor alle steun bij de start van het promotietraject, zodat ik naast de zorg ook mogelijkheid had aan dit proefschrift te werken

Beste Koen Verbeek, dank voor de mooie opmaak van dit proefschrift.

Beste Frederique, dank voor de prachtige cover van dit proefschrift.

Lieve vrienden. Dank voor jullie oprechte interesse in het proefschrift alle jaren dat ik er mee bezig was. Dank voor jullie peptalk als ik dacht dat het allemaal wel heel lang zou gaan duren en dank dat ik de blijdschap bij successen met jullie kon delen. Dank voor soms praktische hulp als op het laatste moment mijn computer niet werkte en er toch een stuk verstuurd moest worden. Dank voor jullie vriendschap!

Lieve Jasmijn, een paar jaar geleden stond ik naast je toen je je proefschrift verdedigde. Nu is het mijn beurt en ik ben heel blij dat je naast mij wilt staan. Ik heb veel respect voor je vaardigheden op het gebied van onderzoek en waardeer vooral de persoonlijke interesse die je altijd hebt. Dank dat je mijn paranimf wilt zijn!

Lieve Wilfred, collega fysiotherapie en onderzoek. Ik vind het fijn dat ik altijd met je kan sparren over onderzoekszaken en waardeer ook je gezelligheid. Met als hoogtepunt de reis voor het congres in Boston! Dank dat je mijn paranimf wilt zijn!

Lieve broers. Wat ben ik blij dat jullie mijn broers zijn. Guido, je bent sociaal, grappig, slim en hebt een ontzettend doorzettingsvermogen. Dat heeft ook mij weer geïnspireerd. Pieter, vooral in de eerste jaren hadden we om de week een etentje waarin het ook heel vaak over de inhoud van het proefschrift ging, je bent kritisch en oprecht geïnteresseerd en het was fijn dat je meedacht over hoe ik bepaalde dingen kon aanpakken, ik heb hier erg van genoten.

Lieve Shirley en Richelle, ik ben heel blij dat jullie deel uit maken van onze familie!

Lieve Gijs en Cathrien, dank voor jullie voortdurende interesse gedurende alle jaren van het promotietraject en de vorderingen daarvan. Dank voor jullie hulp op het gebied van taal- en vormgeving in de laatste fase van het proefschrift en dank voor jullie hulp en steun in het opvangen van Joep, zodat ik aan het proefschrift kon werken.

Lieve pap en mam. Ik weet dat jullie trots zijn, maar ik ben ook trots op jullie. Hoe positief en vol energie jullie in het leven staan. Lieve pap, dank voor het doorzettingsvermogen dat je hebt meegegeven om je best te doen om iets te bereiken. Lieve mam, dank voor je steun en dank dat je in de laatste twee jaar iedere week kwam oppassen, zelfs toen je zelf nog fulltime werkte. Zonder je steun had ik dit proefschrift nooit kunnen afronden.

Lieve Simon! Wat ben ik blij dat we al zo lang samen zijn. Kenmerkend voor jou en onze relatie is dat je mij altijd zal steunen in wat ik doe en motiveert om projecten zoals dit promotietraject aan te gaan. Je hebt altijd ongelofelijk veel vertrouwen in mij en ziet kwaliteiten die ik zelf niet altijd zie. Ik weet niet wat ik zonder jou was, bedankt voor alle jaren en ik hoop dat we nog heel lang kunnen genieten van onze zoons!

Lieve Joep! Sinds jij er bent besef ik dat genieten van jou het allerbelangrijkst is en al het andere er veel minder toe doet. Ik hoop dat je nog altijd zo'n vrolijk en gezellig mannetje blijft!

