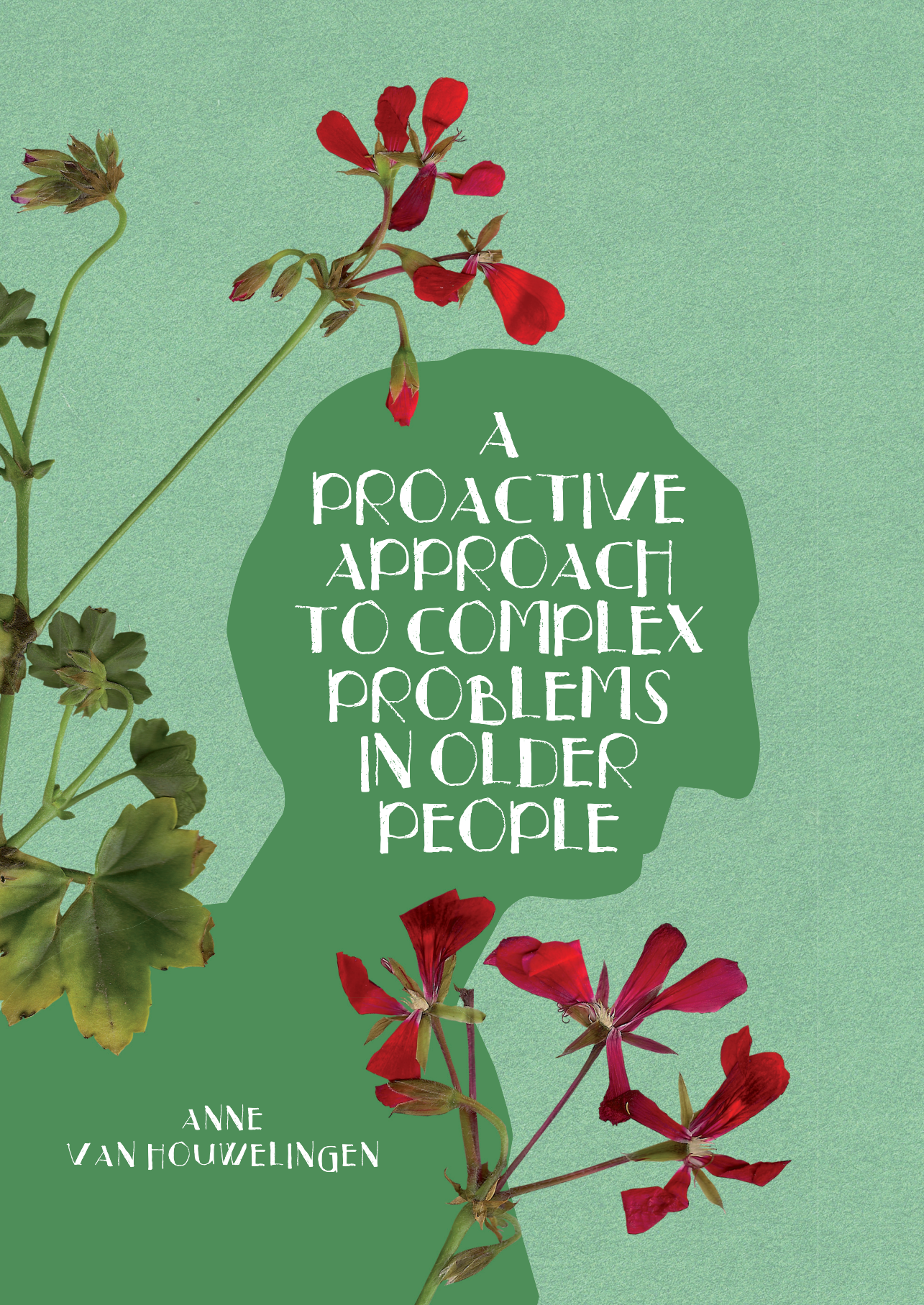
Cover Page

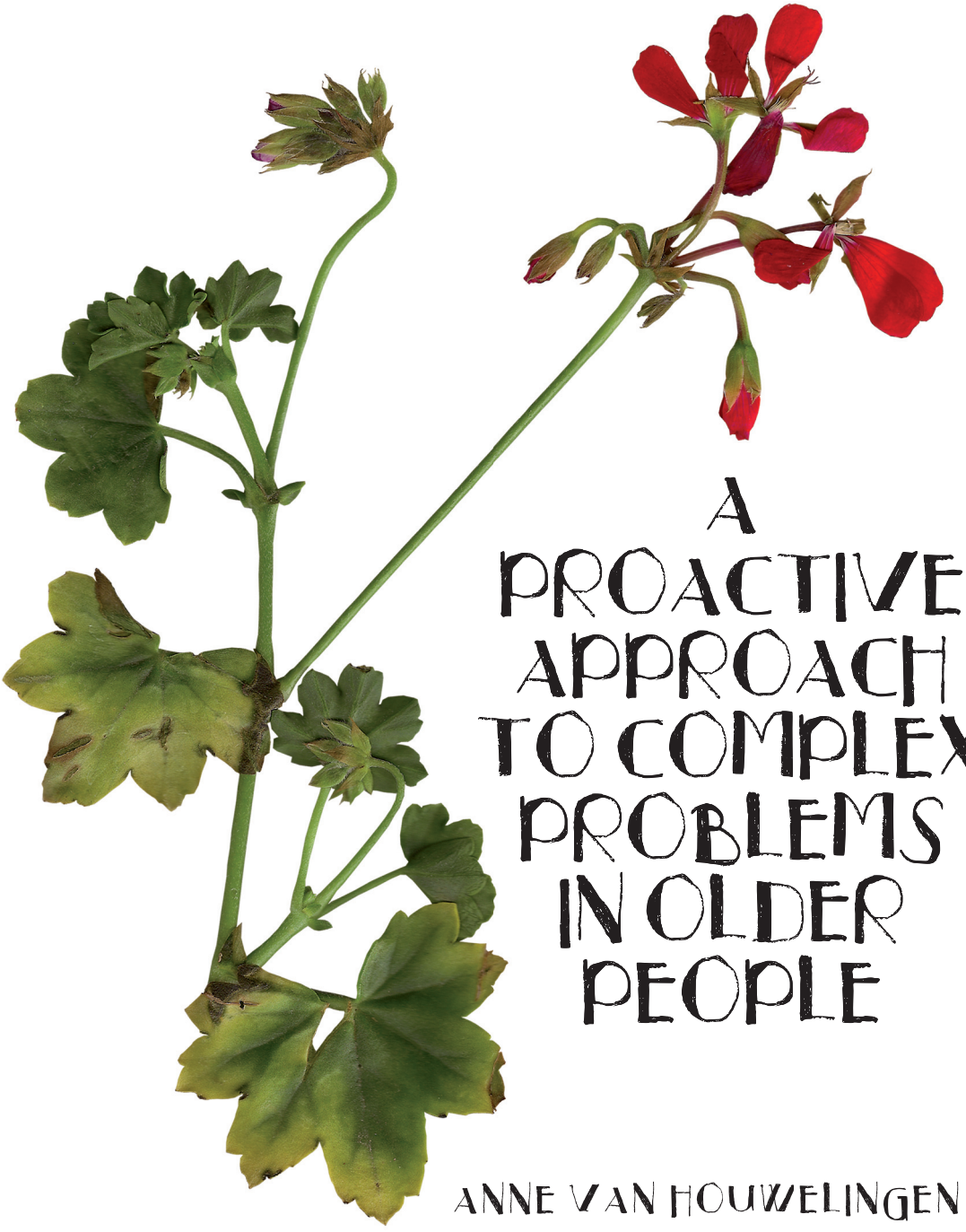
Universiteit Leiden



The handle http://hdl.handle.net/1887/36088 holds various files of this Leiden University dissertation.

Author: Houwelingen, Anne Henriëtte van
Title: A proactive approach to complex problems in older people
Issue Date: 2015-11-05


A PROACTIVE APPROACH TO COMPLEX PROBLEMS IN OLDER PEOPLE
ANNE VAN HOUWELINGEN



A PROACTIVE APPROACH TO COMPLEX PROBLEMS IN OLDER PEOPLE

ANNE VAN HOUWELINGEN

A proactive approach to complex problems in older people
Department of Public Health and Primary Care, Leiden University Medical Center
A.H. van Houwelingen, Leiden, the Netherlands 2015
ISBN: 978-94-6169-658-8

Lay out and printing: Optima Grafische Communicatie, Rotterdam, the Netherlands
Cover design: Emma Stukart

A proactive approach to complex problems in older people

Proefschrift

ter verkrijging van de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof.mr. C.J.J.M. Stolker,
volgens het besluit van het College van Promoties
te verdedigen op donderdag 5 november 2015
klokke 11.15 uur

door

Anne Henriëtte van Houwelingen
geboren te Middelburg
in 1983

PROMOTIECOMMISSIE

Promotor:	Prof. dr. J. Gussekloo
Co-promotores:	Dr. J.W. Blom
	Dr. W.P.J. den Elzen
Overige leden:	Dr. A.J.M. de Craen
	Prof. dr. J.P.J. Slaets (Rijksuniversiteit Groningen)
	Prof. dr. N.J. de Wit (Universiteit Utrecht)

The ISCOPE study was funded by ZonMW (The Netherlands Organization for Health Research and Development). Financial support for printing of this thesis was kindly provided by the SBOH (employer of GP trainees in the Netherlands).

CONTENTS

Chapter 1	General introduction	7
Chapter 2	Disability transitions in the oldest old in the general population. The Leiden 85-plus study	19
Chapter 3	Predictive value of a profile of routine blood measurements on mortality in older persons in the general population: the Leiden 85-plus study	37
Chapter 4	Consequences of interaction of functional, somatic, mental and social problems in community-dwelling older people	55
Chapter 5	Measuring complex problems in older people: clinimetric properties of a postal screening questionnaire	75
Chapter 6	Comparison of three measures to identify older persons with problems on multiple health domains in primary care	95
Chapter 7	Comparison of quadriceps strength and handgrip strength in their association with health outcomes in older adults in primary care	111
Chapter 8	Effectiveness and cost-effectiveness of a proactive, goal oriented, integrated care model in general practice for older people. A cluster randomized controlled trial: Integrated Systematic Care for Older PEople – the ISCOPE study	131
Chapter 9	General discussion	157
Chapter 10	Summary	177
Chapter 11	Samenvatting (Dutch summary)	189

Appendices 201

Appendix 1: ISCOPE screening questionnaire 202

Appendix 2: Additional items suggested by the experts 205

Appendix 3: Framework and content of the training of the intervention group of the ISCOPE study 206

Appendix 4: Format of care plan by the general practitioner for older people with complex problems 208

Appendix 5: Economic evaluation ISCOPE-study 211

Dankwoord 219

Curriculum Vitae 221





GENERAL INTRODUCTION

In 2007, the Dutch College of General Practitioners (DCGP) published a statement on future care for older people in general practice[1]. In 2008 the Dutch government released the National Programme of Elderly Care (NPEC)[2]. Both the DCGP and the NPEC recognised an increasing population of older people with complex problems, for whom health care is poorly coordinated. Both the DCGP and the NPEC introduced proactive integrated care as an answer to poorly coordinated care.

The work presented in this thesis is set within this context of integrated care for older people with complex problems.

This thesis is based on two main research questions:

1) How can older people with complex problems, that might benefit from integrated care, be identified?
2) How effective Is proactive integrated care for older people with complex problems in general practice?

Information on what is already known about these two questions is discussed below.

PROACTIVE IDENTIFICATION OF OLDER PEOPLE WITH COMPLEX PROBLEMS

Most older people have multiple (health) problems. For example, about 20-30% of the population aged 70 years and over has a disability[3]. Additionally, the incidence and prevalence of chronic disease is much higher among the elderly: most older people have at least one chronic disease (69% of people aged $\geq$75 years[4]) and at least 40% of older people aged 75 years and over suffer from multimorbidity (i.e. two or more chronic diseases)[4]. Also, apart from chronic diseases, (minor) ailments, such as memory complaints, restricted mobility, falls, vision and hearing problems and incontinence, increase with age. These ailments tend to have a considerable impact on the daily life of older people. In addition, because of a decreasing number of friends and family, various social problems (such as loneliness) can arise. This implies that most older people will probably have multiples of these functional, somatic, mental and/or social problems, which often interact (Figure 1). These multiple interacting problems in older people are covered by the term complex problems.

To provide integrated care, and to test the hypothesis that older people with complex problems might benefit from integrated care, general practitioners (GPs) need to be able to identify this group of older people.

This identification should preferably be proactive in order to prevent adverse outcomes. Proactive means tending to initiate something rather than reacting when certain events have occurred. In the context of identification of complex problems, proactive

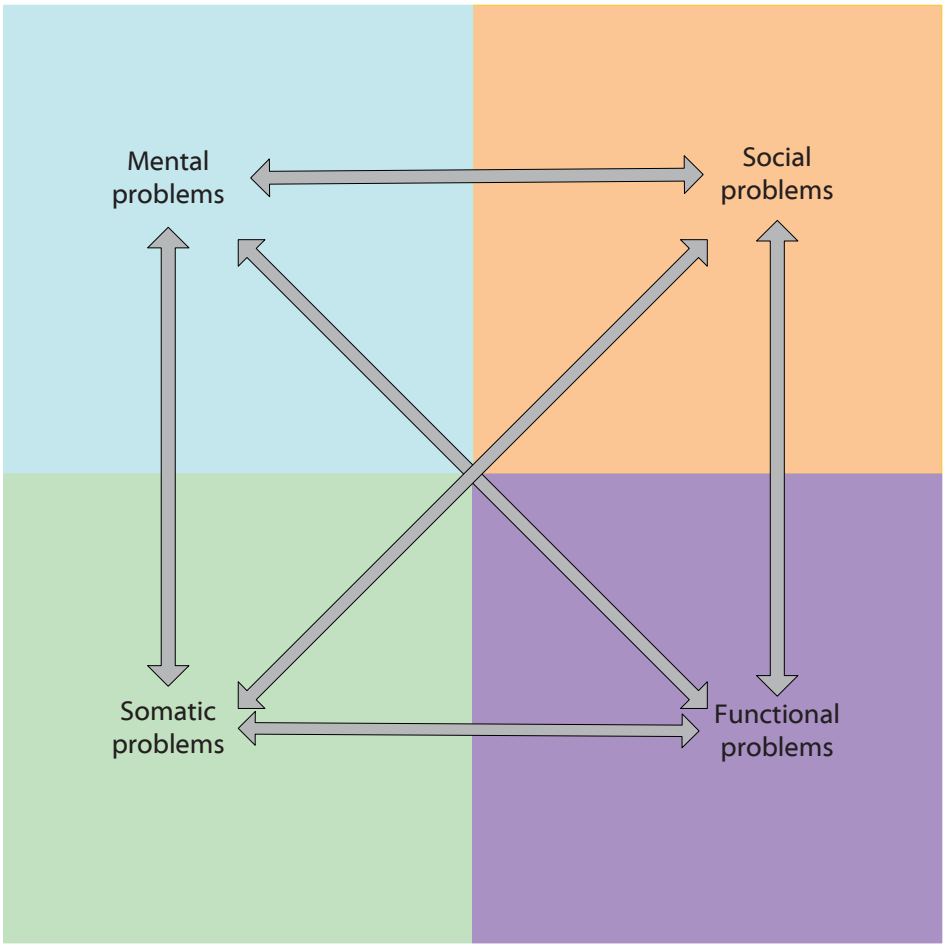


Figure 1. Conceptual model of complex problems in older people.

implies: identification of older people at risk for adverse outcomes rather than reacting to an adverse outcome. With this proactive identification, adverse outcomes might be postponed or even prevented.

Functional decline is an adverse outcome that needs to be proactively identified, because functional decline is an important and certainly undesired adverse outcome for most older people. This is because functional decline leads to disability and, most likely, dependency upon others. Of all older groups of people, older people with complex problems are considered to be at highest risk for functional decline. Therefore, this group of older people needs to be proactively identified.

We tested five measures to proactively identify older people with complex problems, for their feasibility within general practice. These measures included a profile of laboratory

measurements, handgrip- and quadriceps muscle strength, Fried's frailty phenotype criteria[11], the clinical intuition of the GP, and the ISCOPE screening questionnaire. These measures are briefly discussed below.

Laboratory parameters are used by GPs to regularly monitor older persons. Many of these parameters, including C-reactive protein (CRP) level[5], high homocysteine level[6], low high-density lipoprotein-cholesterol (HDL-C)[7], low albumin level[8], low alanine transaminase level[9], low hemoglobin level[10, 11], and poor kidney function (low creatinin clearance)[12], are individually associated with adverse outcomes. An index that combines these parameters into one profile could be a good measure to identify problems in the somatic domain general practice. Since the somatic domain is one of the domains that determine complex problems (Figure 1), and all these domains interact mutually, somatic problems identified by a laboratory profile might also be an effective measure to identify complex problems.

Sarcopenia is the degenerative loss of skeletal muscle associated with aging[13] . Sarcopenia is thought to play a major role in functional decline[14, 15] . Handgrip strength is often used as a measure for sarcopenia and is associated with several adverse health outcomes[16-21], although upper limb muscle strength (measured by quadricpes strength) might be a better reflection of sarcopenia[13]. Measurement of muscle strength is not often used in primary care, but is relatively easy to obtain. Both reduced handgrip- and upper limb muscle strength could be a good measure to identify problems in the somatic domain of complex problems. Therefore the measurement of muscle strength could be feasible to identify complex problems in general practice.

The Fried's frailty phenotype is an internationally recognized and validated measure[11]. This measure aims to identify frailty in older people. Frailty is a term used to describe a biologic syndrome of decreased reserve and resistance to stressors in older people, resulting from cumulative declines across multiple physiologic systems which increase the risk of adverse outcomes[22]. The Fried frailty phenotype criteria define frailty as meeting three or more of the following criteria: 1) unintentional weight loss, 2) self-reported exhaustion, 3) slow walking speed, 4) weak grip strength, and 5) low physical activity level[22]. The Fried frailty phenotype criteria have been widely used in research[22] but are rarely applied in general practice[23]. It is currently unknown whether the Fried frailty phenotype criteria can be used as a measure to identify complex problems in general practice. However, since frailty is a concept which describes the interrelation of multiple health domains in older people, the Fried frailty criteria are potentially suitable for the identification of complex problems.

Most healthcare providers have a clear clinical intuition about the vulnerability of older people. It is expected that the intuition of clinicians will improve when there is a long-term doctor-patient relationship. Since most GPs have a long-term relationship

with their patients and are used to relying on a 'gut feeling' in their diagnostic process[24] the GP's clinical intuition could be an appropriate measure to identify vulnerability in older people[25, 26]. However, it is unknown whether this intuition about vulnerability can be used as an effective measure to identify complex problems.

In addition to these measures which were already available, as a part of this thesis we developed a new measure to identify complex problems in general practice, i.e. a questionnaire with questions covering the four domains of health (functional, somatic, mental and social), known as the ISCOPE screening questionnaire. Based on this questionnaire, older people are considered to have complex problems when they indicate to have problems on three or four of the four domains. Items were partly derived from

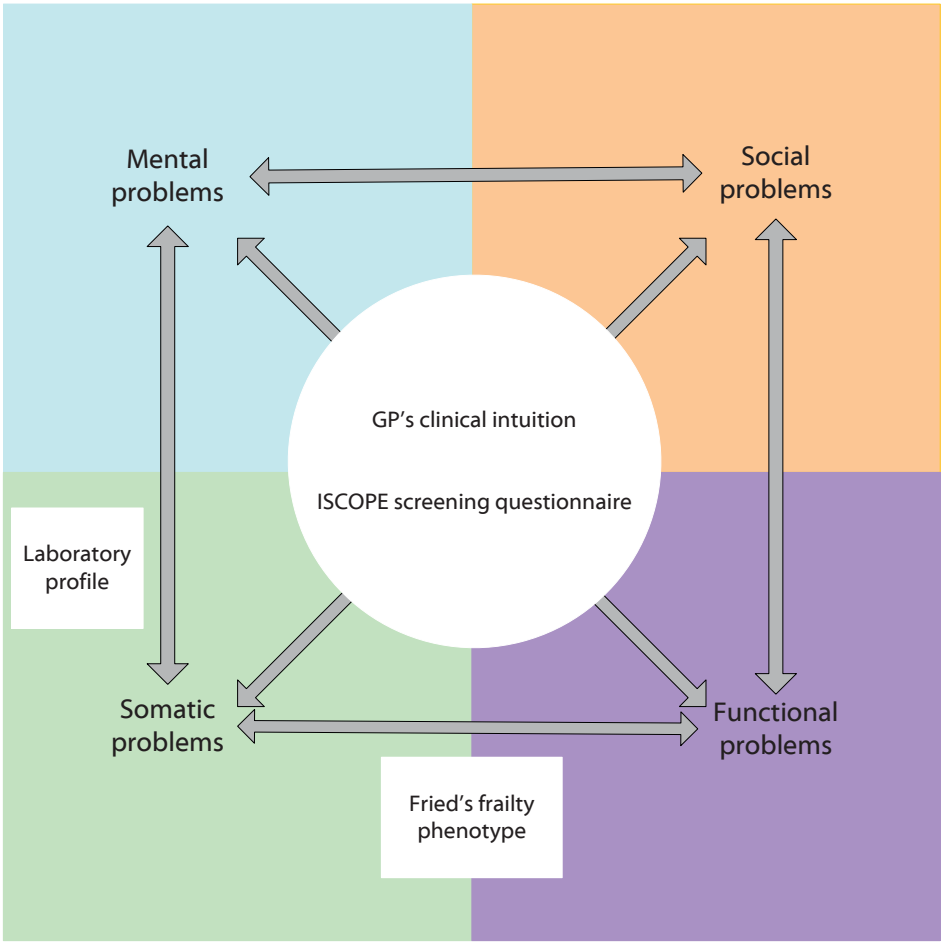


Figure 2. Conceptual model of complex problems in older people, the measures to identify complex problems examined in this thesis are placed in the domains that they aim to measure.

existing identification measures, including the Groningen Frailty Indicator (GFI)[27] and the Identification of Seniors At Risk (ISAR) tool[28].

The five above-described measures can be classified according to the domains of complex problems that they relate to (Figure 2). As only somatic (laboratory) parameters are included in the laboratory profile, it is assumed that they measure primarily somatic problems. Muscle strength is also a somatic parameter and is therefore also assumed to measure somatic problems. In contrast, Fried's frailty phenotype measures somatic problems (unintentional weight loss, self-reported exhaustion and low physical activity level, weak grip strength) as well as functional problems (slow walking speed). The GP's intuition is assumed to relate to all these domains, as a holistic vision on their patients is thought to be characteristic for GPs. Finally, the ISCOPE screening questionnaire aims to identify problems in each health domain.

PROACTIVE INTEGRATED CARE FOR OLDER PEOPLE WITH COMPLEX PROBLEMS IN GENERAL PRACTICE

For several reasons, primary care for older persons with complex problems is often not optimal. Firstly, GPs, multiple medical specialists and (informal) caregivers are usually involved with these older persons; unfortunately they each tend to deal with individual problems separately, and none of these professionals has an overview of all the problems of these older persons. This may lead to fragmented care. Secondly, because disease-specific guidelines do not always apply to older people with complex problems[4], the care processes for this group are often not routine or standard.

It has been suggested that to more optimally address these complex problems, GPs, medical specialists and (informal) caregivers should collaborate – this is known as integrated care. The DCGP issued a statement (which was based on expert opinions), recommending integrated care for older people in general practice, in particular for older people with complex problems[1]. In fact, some evidence is available for the effectiveness of integrated care for older people with complex problems[28-30]. In line with this, most GPs are interested to implement integrated care in their practices.

However, no programs are currently available in the Netherlands for integrated primary care. Therefore, we selected a method that is commonly used by elderly care and rehabilitation physicians in the Netherlands. The reason for this is that, within rehabilitation and nursing home medicine, the therapeutic focus is on function rather than on disease. In other words: therapeutic goals are mainly to restore and maintain functional status. For older people with complex problems, this functionally-oriented care is preferred to the traditional disease-oriented approach, because a diagnosis of a

disease is unlikely to fully depict the severity and nature of the accompanying functional consequences.

Specifically, to support this approach, the GP/physician (who has overall responsibility) in close collaboration with the other healthcare workers (e.g. physiotherapist, psychologist, etc.) formulates a so-called care plan which combines problems on all health domains (functional, somatic, mental and social). This care plan consists of two steps. The first is an inventory of the existing health problems using five categories or problem areas[31]: somatic, activities of daily living, social, psychological and communicative problems (SASPC). The wishes and expectations of the older person about the goals to achieve are explored in a dialogue between the participant and the informal caregivers. The second step is to design the care plan itself, taking the priorities and goals of the older person and informal caregivers as a starting point. Such integrated care plans made by GPs for older people with complex problems could be used to implement integrated care in general practice.

GENERAL AIMS AND OUTLINE OF THIS THESIS

The aims of this thesis were:

1. To test five measures on their feasibility to proactively identify older people with complex problems in general practice
2. To investigate the (cost-) effectiveness of a proactive integrated care plan for older persons with complex problems in general practice.

The Integrated Systematic Care for Older PEople (ISCOPE) study was designed and conducted to explore whether a proactive approach to complex problems in older people (consisting of proactive identification of older people with complex problems as well as an integrated care plan for older people with complex problems) is applicable for GPs in the Netherlands. Additionally, the ISCOPE study was used to investigate measures to identify older persons with complex problems in general practice. To investigate longitudinal identification measures for complex problems we also used the Leiden 85-plus Study, a prospective cohort of 85-year-olds living in Leiden, the Netherlands.

Chapter 2 describes a multistate model to predict disability transitions in the oldest old in the general population.
Chapter 3 examines the predictive value of a profile of routine blood measurements in the Leiden 85-plus Study.
Chapter 4 examines the consequences of the interaction of functional, somatic, mental and social problems in older persons.
Chapter 5 reports on the development, feasibility, internal consistency, construct validity, test-retest reliability and content validity of the ISCOPE screening questionnaire.
Chapter 6 compares the yield of three measures of complex problems in a cross-sectional sample of participants of ISCOPE. The comparison involved the Fried frailty phenotype criteria[11], clinical intuition of the GP, and the ISCOPE screening questionnaire.
Chapter 7 compares handgrip and quadriceps strength in their association with adverse health outcomes in older people in general practice.
Chapter 8 presents the results of the ISCOPE randomized trial, which investigates the effects and costs of a proactive approach in older people with complex problems by general practitioners in the Netherlands.
Chapter 9 is a general discussion of the main results of this thesis. This chapter also focuses on implications for further research on this topic.
Chapter 10 and *Chapter 11* provide a summary of the results of this thesis, in English and Dutch, respectively.
The results of this thesis will contribute to evidence-based care for older people in general practice.

REFERENCES

1. NHG-standpunt Toekomstvisie Huisartsenzorg. Huisartsgeneeskunde voor ouderen. NHG, 2007 . 31-5-2007.
2. De Staatssecretaris van Volksgezondheid Welzijn en Sport mw dr J. Bussemaker. Brief aan de Tweede kamer: Multimorbiditeit en ouderenzorg. 12-11-2007.
3. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. J Gerontol A Biol Sci Med Sci 2004;59(3):255-263.
4. van Weel C, Schellevis FG. Comorbidity and guidelines: conflicting interests. Lancet 2006;367(9510):550-551.
5. Willems JM, Trompet S, Blauw GJ, Westendorp RG, de Craen AJ. White blood cell count and C-reactive protein are independent predictors of mortality in the oldest old. J Gerontol A Biol Sci Med Sci 2010;65(7):764-768.
6. de Ruijter W, Westendorp RG, Assendelft WJ et al. Use of Framingham risk score and new biomarkers to predict cardiovascular mortality in older people: population based observational cohort study. BMJ 2009;338:a3083.
7. Weverling-Rijnsburger AW, Jonkers IJ, van Exel E, Gussekloo J, Westendorp RG. High-density vs low-density lipoprotein cholesterol as the risk factor for coronary artery disease and stroke in old age. Arch Intern Med 2003;163(13):1549-1554.
8. Schalk BW, Visser M, Bremmer MA, Penninx BW, Bouter LM, Deeg DJ. Change of serum albumin and risk of cardiovascular disease and all-cause mortality: Longitudinal Aging Study Amsterdam. Am J Epidemiol 2006;164(10):969-977.
9. Ford I, Mooijaart SP, Lloyd S et al. The inverse relationship between alanine aminotransferase in the normal range and adverse cardiovascular and non-cardiovascular outcomes. Int J Epidemiol 2011;40(6):1530-1538.
10. Culleton BF, Manns BJ, Zhang J, Tonelli M, Klarenbach S, Hemmelgarn BR. Impact of anemia on hospitalization and mortality in older adults. Blood 2006;107(10):3841-3846.
11. den Elzen WP, Willems JM, Westendorp RG, de Craen AJ, Assendelft WJ, Gussekloo J. Effect of anemia and comorbidity on functional status and mortality in old age: results from the Leiden 85-plus Study. CMAJ 2009;181(3-4):151-157.
12. van Bemmel T, Woittiez K, Blauw GJ et al. Prospective study of the effect of blood pressure on renal function in old age: the Leiden 85-Plus Study. J Am Soc Nephrol 2006;17(9):2561-2566.
13. Cruz-Jentoft AJ, Baeyens JP, Bauer JM et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing 2010;39(4):412-423.
14. Morley JE, Baumgartner RN, Roubenoff R, Mayer J, Nair KS. Sarcopenia. J Lab Clin Med 2001;137(4):231-243.
15. Rolland Y, Czerwinski S, Abellan Van KG et al. Sarcopenia: its assessment, etiology, pathogenesis, consequences and future perspectives. J Nutr Health Aging 2008;12(7):433-450.
16. Femia EE, Zarit SH, Johansson B. Predicting change in activities of daily living: a longitudinal study of the oldest old in Sweden. J Gerontol B Psychol Sci Soc Sci 1997;52(6):294-302.
17. Giampaoli S, Ferrucci L, Cecchi F et al. Hand-grip strength predicts incident disability in non-disabled older men. Age Ageing 1999;28(3):283-288.

18. Hairi NN, Cumming RG, Naganathan V et al. Loss of muscle strength, mass (sarcopenia), and quality (specific force) and its relationship with functional limitation and physical disability: the Concord Health and Ageing in Men Project. J Am Geriatr Soc 2010;58(11):2055-2062.
19. Rantanen T, Volpato S, Ferrucci L, Heikkinen E, Fried LP, Guralnik JM. Handgrip strength and cause-specific and total mortality in older disabled women: exploring the mechanism. J Am Geriatr Soc 2003;51(5):636-641.
20. Laukkanen P, Heikkinen E, Kauppinen M. Muscle strength and mobility as predictors of survival in 75-84-year-old people. Age Ageing 1995;24(6):468-473.
21. Newman AB, Kupelian V, Visser M et al. Strength, but not muscle mass, is associated with mortality in the health, aging and body composition study cohort. J Gerontol A Biol Sci Med Sci 2006;61(1):72-77.
22. Fried LP, Tangen CM, Walston J et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56(3):M146-M156.
23. Drey M, Wehr H, Wehr G et al. The frailty syndrome in general practitioner care: a pilot study. Z Gerontol Geriatr 2011;44(1):48-54.
24. Stolper E, Van de Wiel M, Van Royen P, Van de Wiel M, Van der Weijden T, Dinant GJ. Gut feelings as a third track in general practitioners' diagnostic reasoning. J Gen Intern Med 2011;26(2):197-203.
25. Drewes YM, Koenen JM, de Ruijter W et al. GPs' perspectives on preventive care for older people: a focus group study. Br J Gen Pract 2012;62(604):765-772.
26. Grant RW, Ashburner JM, Hong CC, Chang Y, Barry MJ, Atlas SJ. Defining Patient Complexity From the Primary Care Physician's Perspective A Cohort Study. Ann of Intern Med 2011;155(12):797-804.
27. Peters LL, Boter H, Buskens E, Slaets JP. Measurement Properties of the Groningen Frailty Indicator in Home-Dwelling and Institutionalized Elderly People. J Am Med Dir Assoc 2012;13(6):546-551.
28. Salvi F, Morichi V, Grilli A et al. Predictive validity of the Identification of Seniors At Risk (ISAR) screening tool in elderly patients presenting to two Italian Emergency Departments. Aging Clin Exp Res 2009;21(1):69-75.
29. Beswick AD, Rees K, Dieppe P et al. Complex interventions to improve physical function and maintain independent living in elderly people: a systematic review and meta-analysis. Lancet 2008; 371 (9614):725-735.
30. Lin JS, Whitlock EP, Eckstrom E et al. Challenges in synthesizing and interpreting the evidence from a systematic review of multifactorial interventions to prevent functional decline in older adults. J Am Geriatr Soc 2012;60(11):2157-2166.
31. Hertogh CMPM., Deerenberg-Kessler W, Ribbe MW. The problem-oriented multidisciplinary approach in Dutch nursing home care. Clinical Rehabilitation 1996;10(2):135-142.



2

DISABILITY TRANSITIONS IN THE OLDEST OLD IN THE GENERAL POPULATION. THE LEIDEN 85-PLUS STUDY

Anne H. van Houwelingen, Ian D. Cameron, Jacobijn Gussekloo, Hein Putter, Susan Kurrle, Anton J.M. de Craen, Andrea B. Maier, Wendy P.J. den Elzen, and Jeanet W. Blom

Age (Dordr). 2014 Feb;36(1):483-93. doi: 10.1007/s11357-013-9574-3.

ABSTRACT

Transitions between disability states in older people occur frequently. This study investigated predictors of disability transitions in the oldest old and was performed in the Leiden 85-plus Study, a population-based prospective cohort study among 597 participants aged 85 years.

At baseline (age 85 years), data on socio-demographic characteristics and chronic diseases were obtained. Disabilities in basic activities of daily living (BADL) and instrumental activities of daily living (IADL) were measured annually for 5 years with the Groningen Activities Restriction Scale (GARS). Mortality data were obtained. A statistical multi-state model was used to assess the risks of transitions between no disabilities, IADL disability, BADL disability and death.

At baseline, 299 participants (50.0%) were disabled in IADL only and 155 participants (26.0%) were disabled in both BADL and IADL. During 5-year follow-up, 374 participants (62.6%) made > 1 transition between disability states, mostly deterioration in disability. Males had a lower risk of deterioration (Hazard ratio [HR] 0.75 [95% CI 0.58-0.96]) compared to females. No gender differences were observed for improvement (HR 0.64 [95% CI 0.37-1.11]), Participants with depressive symptoms were less likely to improve (HR 0.50 [95%CI 0.28-0.87]). Participants with depressive symptoms (HR 1.46 [95% CI 1.12-1.91]), > 1 chronic disease (HR 1.60 [95% CI 1.27-2.01), and with cognitive impairment (HR 1.60 [95% CI 1.20-2.13] had the highest risk of deteriorating.

Disability is a dynamic process in the oldest old. Deterioration is more common than improvement. Older men are less likely to deteriorate than women. The presence of depressive symptoms, chronic disease and cognitive impairment predicts deterioration.

ABBREVIATIONS

IADL: Instrumental Activities of Daily Living
BADL: Basic Activities of Daily living
COPD: Chronic obstructive pulmonary disease
ATC: Anatomic Therapeutic Chemical
MMSE: Mental State Examination
GDS-15: 15-item geriatric depression scale
GARS: Groningen Activities Restriction Scale
PASW: Predictive Analytics Software
HR: Hazard Ratio

INTRODUCTION

Disability in older people is associated with dependency, morbidity, and shorter life expectancy[1,2]. As the population in the Western world is ageing[3,4], the number of older people facing disability will increase in the coming decades. This increasing prevalence of disability will be accompanied by rising healthcare costs, since care for disabled persons is more costly than care for non-disabled persons[5,6]. Therefore, disability becomes increasingly important for older people, their caregivers, and policymakers.

New preventive strategies directed at disability could diminish the burden of disability. When considering the introduction of new strategies, it is important to know which subgroup of older people are candidates for prevention of disability. Previous research has shown that sex[7], level of education[8], cognitive decline[9, 10], physical frailty[11, 12], chronic disease[10, 13], prior disability history[14], and depressive symptoms[13, 15] contribute to changes in disability.

Several studies[7, 11, 12, 16-18] including the Precipitating Events Project[19] found that disability is not a static state, but has a dynamic nature, which means that people can move in and out of disability, with continuous transitions between states of disability. However, most studies focused on transitions in disability in basic activities of daily living (BADL) in older individuals without disability. Less attention has been paid to transitions between disability in BADL and disability in instrumental activities of daily living (IADL) in older people in the general population[7, 16]. Moreover, most studies tended to focus on younger elderly, so that data on disability in individuals aged ≥ 85 years are scarce[20].

This study investigates the transitions between no disability in BADL and IADL, and IADL disability, BADL disability and death, and determines predictors of these transitions in disability states in the oldest old in the general population.

METHODS

Study population

This study was conducted within the Leiden 85-plus Study, an observational population-based prospective cohort study of 85-year old inhabitants of Leiden, the Netherlands. Between 1997 and 1999, 705 inhabitants of Leiden reached the age of 85 years and were eligible for participation. Of these, 14 died before enrolment and 92 refused to participate, resulting in a study population of 599 participants (response rate 87%). No selection criteria for health and demographic characteristics were applied[21].

Participants were followed for five years until the age of 90 years or until death. At baseline and annually thereafter, all participants were visited at their place of residence, where face-to-face interviews were conducted, cognitive testing was performed, and

information on income, education and disabilities in BADL and IADL was obtained. For the present study, participants with missing BADL and IADL measurements at baseline were excluded (n=2) resulting in a study population of 597 participants. All participants gave informed consent; for participants with severe cognitive impairment, informed consent was obtained from a proxy. The Medical Ethics Committee of Leiden University Medical Centre approved the study.

Study parameters

Predictors

Sociodemographic factors

During baseline interviews, a research nurse collected information on sex, residency, income, and level of education.

Presence of chronic diseases

Information on participants' medical history was obtained by standardized interviews with their treating general practitioner or elderly care physician, and/or pharmacy records. We obtained clinical information on the presence of diabetes mellitus, chronic obstructive pulmonary disease (COPD), Parkinson's disease, history of stroke and myocardial infarction, cancer, arthritis and hip fracture. COPD was considered present when the diagnosis COPD was reported by the treating physician or when lung medication (Anatomic Therapeutic chemical [ATC] code R03) was used at age 85 years. The presence of diabetes mellitus was based on the diagnosis of the treating physician, a non-fasting glucose level >200 mg/dL, or the use of anti-diabetic medication.

Cognitive function

Cognitive function was measured with the Mini-Mental State Examination (MMSE) with scores ranging from 0 to 30[22]. Cognitive impairment was considered present when the MMSE score was below 24 points.

Depressive symptoms

The 15-item geriatric depression scale (GDS-15) was used as a screening instrument for depression[23]. As the validity and the reliability of the GDS-15 may be reduced in participants with severe cognitive impairment, this questionnaire was restricted to those with MMSE scores above 18 points. Depressive symptoms were considered present when the GDS-15 score was 4 points or more. This cut-off was used because of its high sensitivity and its acceptable specificity for depressive symptoms, which has been found in a previous study using the same study setting[24].

Outcome

Functional status

Disability in BADL and IADL was measured annually with the Groningen Activities Restriction Scale (GARS)[25]. The GARS is a questionnaire that assesses disabilities in competence in nine BADL items and nine IADL items. The GARS is extensively validated in various study populations and has satisfactory clinimetric properties; the test-retest reliability of the GARS-3 was 0.71[26].

The BADL items included: walk inside the house, get up and out of bed, get in and out of a chair, visit the toilet, wash hands and face, wash body, dress and undress, eat and drink, and prepare breakfast[27]. The IADL items included: light housework, heavy cleaning, wash and iron clothes, clean and make the bed, prepare a hot meal, climbing/descending stairs, get around outdoors, do the groceries, and attend to feet and toenails[27]. Questions were phrased 'Can you fully independently…?' We dichotomized the answers into a score of 0 (cannot or only with help from others) or 1 (yes fully independently, with or without difficulty). Disability in BADL or IADL was considered present when a participant responded 'Cannot or only with help from others' on any BADL or IADL item, respectively. The dichotomizing of BADL en IADL was done because no universal cut-off points of the GARS are known.

Mortality

Dates of death were obtained from municipal registries.

Statistical analysis

Descriptive statistics

Baseline characteristics and the prevalence of IADL and BADL disability at baseline and during follow-up are presented as number (percentage).

Multi-state model

Multi-state analysis was used to assess the participants' risk for making transitions between states of disability. Our multi-state representation of disability included four states: 1) no disability in either BADL or IADL; 2) disability in IADL; 3) disability in both BADL and IADL, and 4) death (Figure 1). Death was included as a competing risk in this model. Since the transition between BADL disability and no disability was observed very rarely, we did not include this transition in the multi-state model.

Transition hazards were first estimated without the inclusion of covariates, then also with the inclusion of covariates. The Aalen-Johansen estimator[28] was used to obtain state occupation probabilities from the transition hazards. The baseline transition haz-

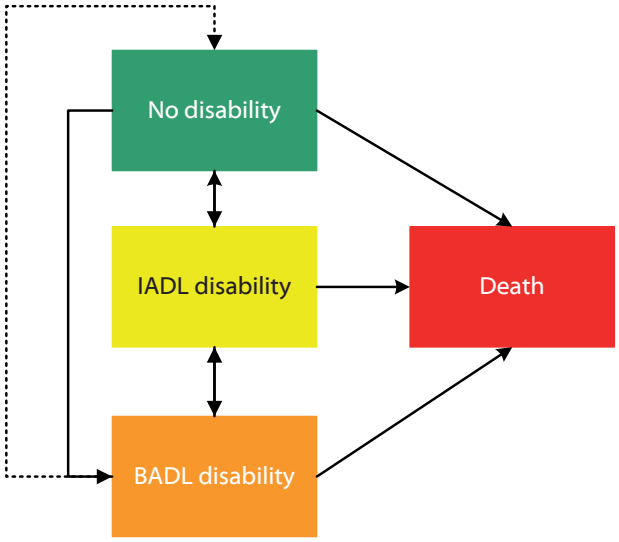


Figure 1. Multi-state representation of the stages of disability. The boxes represent the four stages. The *solid arrows* represent the observed transitions; the *dotted arrow* represents a possible transition that was very rare in this study population and was therefore excluded from the multi-state model.

ards of all transitions going into the "death" state were assumed to be proportional[29], thus allowing the estimation of hazard ratios of IADL and BADL disability on mortality, compared to having no disability. Estimating covariate effects for all transitions separately would yield too unstable estimates because of rare events for some transitions. Therefore, we hypothesized that the effect of a covariate would be similar in the transition from no disability to IADL disability and from IADL disability to BADL disability, since both these transitions represent deterioration in disability state. Similarly, we assumed that the effect of covariates would be similar in the transition from IADL disability to no disability and from BADL disability to IADL disability, since these transitions represent an improvement in disability state. Moreover, the effect of covariates was also assumed to be the same for transitions from no disability to death, and from IADL disability or BADL disability to death. Therefore, we used a simplified model with deteriorating transitions, improving transitions, and transitions to death. Preliminary analyses showed that this simplification did not result in a model with worse fit.

To study the effect of sex, living situation, income, educational level, presence of chronic disease, cognitive impairment and depressive symptoms on transitions between disability states, we used these predictors as covariates in the simplified model. Sex, income, education level, living alone and presence of chronic diseases were included as fixed variables. In the model, cognitive function and depressive symptoms were included as time-dependent variables (i.e. each yearly measurement was included in the model)

Descriptive statistics were computed using PASW 17.0 for Windows. The package mstate[30] version 0.2.5, for R version 2.12.0[31] was used for the multi-state analysis. A p-value of <0.05 was considered statistically significant.

RESULTS

Study population

Table 1 presents the baseline characteristics of the study population at age 85 years. One third of the population was male and 18% was living in a long-term care facility. Of all participants, 118 (23.6 %) had depressive symptoms, 183 (30.7%) had cognitive impairment (of which 58 had a clinical diagnosis of dementia by their GP) and almost 70% had at least one chronic disease. At the end of follow-up, 277 participants aged 90 years were interviewed. During the 5-year follow-up period, 41 participants refused further participation and 279 participants died.

Table 1. Baseline characteristics of the participants at age 85 years.

	n=597
Sociodemographic	
Men	202 (33.8)
Institutionalized	107 (17.9)
Low income (<750 euro monthly)	295 (49.3)
Low education level (6 years of primary school)	207 (34.6)
General health	
Depressive symptoms (GDS-15 ≥ 4 pts)	118 (23.6)
Cognitive impairment (MMSE < 24 pts)	183 (30.7)
Chronic diseases	
≥1 chronic disease	414 (69.1)
Cancer	104 (17.4)
Myocardial infarction	63 (10.6)
Stroke	61 (10.2)
Diabetes	86 (14.4)
Chronic Obstructive Pulmonary Disease	70 (11.7)
Parkinson's disease	15 (2.5)
Arthritis	193 (32.3)
History of hip fracture	38 (6.4)

Data are numbers and percentages

* GDS-15= Geriatric Depression Scale 15 items; MMSE = Mini-Mental State Examination; Chronic diseases included cancer, myocardial infarction, stroke, diabetes, chronic obstructive pulmonary disease, Parkinson's disease, arthritis and history of hip fracture

Prevalence of disability

At age 85 years, 143 participants (24%) had no disability in IADL and BADL, 299 participants (50%) had IADL disability only, and 155 participants (26%) had BADL disability. Participants with IADL disability most often reported being unable to do heavy household activities compared with their counterparts with IADL disability only. Being unable to wash and dry the whole body was the most frequently reported BADL item for this group (appendix table 3). The prevalence of BADL disability increased with age to 58% at age 90 years. The prevalence of IADL disability and the prevalence of no disability decreased during follow-up to 35% and 6%, respectively, at age 90 years (Figure 2). As expected, at each year, all participants with BADL disability also had IADL disability, showing the hierarchical relationship between the two forms of disability.

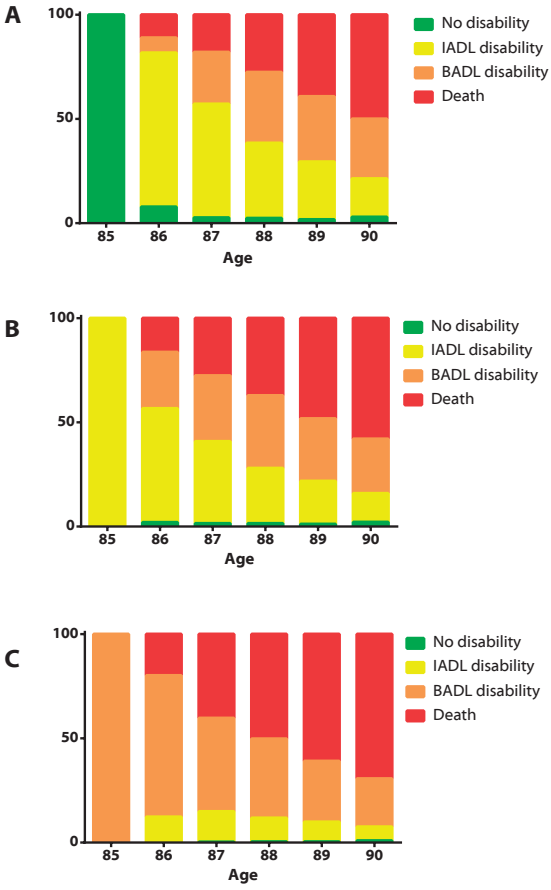


Figure 2. Estimated transition probabilities of the three states of disability and death during follow-up depending on the disability state at baseline (age 85): a no disability at baseline, b IADL disability at baseline, and c BADL disability at baseline.

Disability states during follow-up

Of the 277 participants (46.4%) who were alive at 5-years follow-up, 205 (41.2%) made one or more transitions between disability states and 72 (12.0%) were stable in their baseline disability state. Of these 72 participants, five (0.8%) remained free of disability during follow-up, 37 (6.2%) had stable IADL disability, and 30 (5.0%) had stable BADL disability. Of the 277 participants who were alive at 5 year follow-up, 83 (30%) had no disability at baseline, 150 (54.2%) had IADL-disability and 44 (15.9%) had BADL-disability at baseline.

Of the 279 participants who died during follow-up (53.4%), 110 (18.4%) were stable in their baseline disability state and 169 participants (28.3%) had made one or more transitions between disability states before death.

In total, 374 participants (69.5%) made one or more transitions between disability states and 182 (30.5%) were stable in their baseline disability state until death or until they reached the age of 90 years. The 374 participants who made one or more transitions between disability states made 579 transitions in total (i.e. mean 1.6 transitions per participant); most of these transitions were directed at deteriorating disability (513 deteriorating transitions and 66 improving transitions). Of these 374 participants, 83 (13.9%) improved in disability state at some time during follow-up, 29 (4.9%) improved from IADL disability to no disability state, and 54 participants (9.0%) improved from BADL disability to IADL disability. The remaining 291 participants made transitions directed at greater disability only.

Transitions between states

The relative risk for participants with IADL disability to deteriorate to BADL disability was HR 6.21 (95% CI 3.35-11.35), compared to participants with no disability to deteriorate to BADL disability. Moreover, an increase in disability was associated with an increased risk of death. The relative mortality risk for participants with IADL disability was HR 1.44 [95% CI 0.97-2.63] and for participants with BADL disability was HR 4.20 [95% CI 2.31-7.53], both compared to participants with no disability at any time during follow-up.

Predictors of transitions

Table 2 shows the predictive value of sociodemographic and health determinants on disability transitions. Males had a higher death rate compared to females, but were more stable with respect to their disability state; they had a lower risk of deteriorating (HR 0.75 [95% CI 0.58-0.96] p=0.03). No gender differences were observed for improving (HR 0.64 [0.37-1.11] p=0.11) in disability state. Higher income (more than state pension), higher education level (more than primary school) and living alone were not associated with improvement or deterioration in disability state. Participants with depressive symptoms (GDS-15 score >4) had a lower risk of transition to an improved disability state (HR 0.50

[95% CI 0.28-0.87], p=0.01), and a higher risk of transition to a deteriorated disability state (HR 1.46 [1.12-1.91], p <0.01) compared to participants without depressive symptoms. Participants with and without depressive symptoms had similar mortality rates. Chronic disease and cognitive impairment (MMSE score <24) were associated with a higher risk of deteriorating in disability state (HR 1.60 [95% CI 1.27-2.01] and HR 1.60 [95% CI 1.20-2.13], respectively, p<0.01) and a higher death rate (HR 1.48 [95% CI 0.96-2.26] p=0.07 and HR 1.64 [1.12-2.39 p=0.01), but were not associated with an increased or decreased risk for improvement in disability state.

Table 2. Multi-variate prediction of improvement in disability state, deterioration in disability state and death by health characteristics over the 5-year follow-up.

	Relative risk of transition to improved disability state		Relative risk of transition to deteriorated disability state		Relative risk of transition to death	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Men (ref: women)	0.64 (0.37-1.11)	0.11	0.75 (0.58-0.96)	0.03	2.10 (1.44-3.07)	<0.01
Low income (< 750 euro monthly) (ref:> 750 euro monthly)	1.07 (0.67-1.71)	0.77	1.10 (0.87-1.39)	0.41	0.97 (0.67-1.41)	0.88
Low education level (6 years of primary school) (ref: > primary school)	1.21 (0.74-1.98)	0.45	0.97 (0.77-1.23)	0.82	0.94 (0.64-1.38)	0.76
Living alone (ref: living with someone)	1.48 (0.92-2.39)	0.11	1.13 (0.88-1.45)	0.32	0.94 (0.64-1.38)	0.73
Chronic disease (ref: no chronic disease)	0.76 (0.47-1.24)	0.27	1.60 (1.27-2.01)	<0.01	1.48 (0.96-2.26)	0.07
Cognitive impairment (MMSE <24 pts) (ref: MMSE ≥24)	0.62 (0.36-1.09)	0.10	1.60 (1.20-2.13)	<0.01	1.64 (1.12-2.39)	0.01
Depressive symptoms (GDS-15 ≥4 pts) (ref: GDS <4)	0.50 (0.28-0.87)	0.01	1.46 (1.12-1.91)	<0.01	1.09 (0.75-1.58)	0.64

CI= confidence interval; GDS-15= Geriatric Depression Scale 15 items; MMSE = Mini-Mental state Examination; HR=Hazard ratio

Hazard ratios were estimated with a multistate Cox model. Sex, income, education level, living alone and presence of chronic diseases were included as fixed variables. Cognitive function and depressive symptoms were included as timedependent variables

Chronic diseases included cancer, myocardial infarction, stroke, diabetes, chronic obstructive pulmonary disease, Parkinson's disease and history of hip fracture

DISCUSSION

The present study shows that, among the oldest old in the general population, disability in BADL and IADL is a dynamic process with frequent transitions between disability states. In this study, the most important predictors for transition from no disability to both IADL and BADL disability states were the presence of depressive symptoms, chronic disease and cognitive impairment. Men had a higher mortality rate compared to women, but were more stable with respect to their disability state. Whilst transitions to greater disability and death were much more common than improvements in disability, a small number of very old persons do improve in disability status. Recovery from any acute pathological condition or injury could partly explain this. An intriguing result of this study is that the proportion of older people without any disability that shows some functional decline between age 85 and age 86 is almost 80% (similarly from age 86 to age 87). This may be explained by the fact that people of this advanced age are known to decline in function very rapidly[32].

Our results in persons aged ≥ 85 years confirm those of other studies on transitions between disability states[7, 11, 12, 16-18, 33]. However, unlike other studies which presented high recovery rates[7, 8, 11, 12, 16, 18], our study participants infrequently recovered from disability. Three of these previous studies were performed in the same study population[11, 12, 18] of the Precipitating Events Project[19]. Of the other three, one was restricted to moderately and severely disabled women[8], and one to disabled patients aged 65 years and older registered for home services[7]. Only the population-based study by Peres and colleagues and the study of Mor en colleagues are comparable with the present study[16, 33]. In these studies, similar results were found for people of old age (80 years and over). The infrequent recovery in our study might thus be explained by the old age of our study population.

Moreover since IADL disability is highly prevalent among the very elderly[27], it is less likely that the oldest old fully recover to a non-disabled state. Therefore, the transition from BADL disability to no disability was too uncommon to include in the multistate model. In contrast to the abovementioned studies, we had yearly intervals between disability assessments.

Our predictors of transitions in disability state are generally in line with others, who also found that males are more stable with respect to their disability state than females. This has been described as the health-survival paradox in the very old: i.e. men seem to be healthier than women but die earlier[34]. The biological mechanism underlying this paradox has yet to be unravelled.

The fact that both cognitive impairment and the presence of chronic illness predicted a greater risk of deterioration in disability confirms the results of previous studies on this topic[7, 9, 10, 13, 16, 35]. Older people with depressive symptoms were at higher risk of de-

teriorating in disability state, and had a lower chance of improvement. This is consistent with others[15, 36] and provides evidence that recognition and treatment of depressive symptoms in the oldest old could lead to a reduction of the burden of disability.

The aim of our study was to investigate predictors of disability status in the general population at large. Our study population therefore also included persons living in care homes or nursing homes. Since persons living in these institutions are not likely to improve in disability status, and may often have an increased risk of depression[37], comorbidity and cognitive impairment, this may have resulted in an underestimation of the predictive value of depression, comorbidity and cognitive impairment on the change in disability status for community-dwelling elderly.

Since this study assesses the predictive value of the determinants on disability changes, the results should not be etiologically interpreted. For example: the predictive value of depression on disability has been extensively studied, but a causal relationship has not been identified yet[38].

The results of our study are important for several reasons. First, people aged ≥ 85 years are the fastest growing segment of the general population, and data on disability in this population are limited[20]. This age group is often excluded from clinical trials and preventive interventions, and is sometimes undertreated[39-41]. Therefore, the results of this study in this specific population provide valuable information to help develop preventive strategies directed towards disability in this age group. Second, the results could also have implications for geriatric rehabilitation programs.

Strengths and limitations

Our study has several strengths. The Leiden 85-plus Study is a longitudinal population-based cohort study with no exclusion criteria and almost complete follow-up for mortality. A total of 87% of the oldest old in the population participated in this study. This high participation rate adds to the external validity of our results. Moreover, the longitudinal design with repeated measurements of competence in IADL and BADL allowed us to demonstrate the dynamic process of disability in this unique sample of very old participants. Another strength of our study is that we included both IADL and BADL disability and the transitions between these disability states, healthy, and death. In addition, the use of a multi-state model allowed us to include more than one transition per participant, and allowed inclusion of death as a competing risk and separate outcome.

A limitation of our study is its relatively small sample size. A larger study would allow us to investigate the predictive effect of more covariates and to perform subgroup analyses. Another limitation is that, due to the dichotomizing of disability in this study, small changes in disability status may be unnoticed by the multi-state model. This relates to the limits of the multi-state model, which does not allow inclusion of continuous

variables. Moreover, since the multistate model will be unstable when too many predictors are added, we added a predictor which was based on a score of all chronic diseases.

CONCLUSION

Disability remains a dynamic process in the oldest old in the general population. Transitions to a deteriorating disability status are more common than transitions to an improved disability status. Older men are less likely to deteriorate in disability status than women. The presence of depressive symptoms, chronic disease and cognitive impairment predict deterioration in disability. Further research is needed to investigate whether older people with a higher risk for deterioration would benefit from preventive programs or interventions designed to reverse disability.

REFERENCES

1. Cigolle CT, Langa KM, Kabeto MU, Tian Z, Blaum CS. Geriatric conditions and disability: the Health and Retirement Study. Ann Intern Med 2007;147(3):156-164.
2. Manton KG, Gu X, Lowrimore GR. Cohort changes in active life expectancy in the U.S. elderly population: experience from the 1982-2004 National Long-Term Care Survey. J Gerontol B Psychol Sci Soc Sci 2008;63(5):S269-S281.
3. Christensen K, Doblhammer G, Rau R, Vaupel JW. Ageing populations: the challenges ahead. Lancet 2009;374(9696):1196-1208.
4. Lutz W, Sanderson W, Scherbov S. The coming acceleration of global population ageing. Nature 2008;451(7179):716-719.
5. Guralnik JM, Alecxih L, Branch LG, Wiener JM. Medical and long-term care costs when older persons become more dependent. Am J Public Health 2002;92(8):1244-1245.
6. Harrow BS, Tennstedt SL, McKinlay JB. How costly is it to care for disabled elders in a community setting? Gerontologist 1995;35(6):803-813.
7. Nikolova R, Demers L, Beland F, Giroux F. Transitions in the functional status of disabled community-living older adults over a 3-year follow-up period. Arch Gerontol Geriatr 2011;52(1):12-17.
8. Boyd CM, Ricks M, Fried LP et al. Functional decline and recovery of activities of daily living in hospitalized, disabled older women: the Women's Health and Aging Study I. J Am Geriatr Soc 2009;57(10):1757-1766.
9. Tas U, Verhagen AP, Bierma-Zeinstra SM, Odding E, Koes BW. Prognostic factors of disability in older people: a systematic review. Br J Gen Pract 2007;57(537):319-323.
10. Drewes YM, den Elzen WP, Mooijaart SP, De Craen AJ, Assendelft WJ, Gussekloo J. The effect of cognitive impairment on the predictive value of multimorbidity for the increase in disability in the oldest old: the Leiden 85-plus Study. Age Ageing 2011;40(3):352-357.
11. Hardy SE, Dubin JA, Holford TR, Gill TM. Transitions between states of disability and independence among older persons. Am J Epidemiol 2005;161(6):575-584.
12. Hardy SE, Gill TM. Factors associated with recovery of independence among newly disabled older persons. Arch Intern Med 2005;165(1):106-112.
13. Stuck AE, Walthert JM, Nikolaus T, Bula CJ, Hohmann C, Beck JC. Risk factors for functional status decline in community-living elderly people: a systematic literature review. Soc Sci Med 1999;48(4):445-469.
14. Hardy SE, Allore HG, Guo Z, Dubin JA, Gill TM. The effect of prior disability history on subsequent functional transitions. J Gerontol A Biol Sci Med Sci 2006;61(3):272-277.
15. Barry LC, Allore HG, Bruce ML, Gill TM. Longitudinal association between depressive symptoms and disability burden among older persons. J Gerontol A Biol Sci Med Sci 2009;64(12):1325-1332.
16. Peres K, Verret C, Alioum A, Barberger-Gateau P. The disablement process: factors associated with progression of disability and recovery in French elderly people. Disabil Rehabil 2005;27(5):263-276.
17. Gill TM, Allore HG, Gahbauer EA, Murphy TE. Change in disability after hospitalization or restricted activity in older persons. JAMA 2010;304(17):1919-1928.
18. Hardy SE, Gill TM. Recovery from disability among community-dwelling older persons. JAMA 2004;291(13):1596-1602.
19. Gill TM, Desai MM, Gahbauer EA, Holford TR, Williams CS. Restricted activity among community-living older persons: incidence, precipitants, and health care utilization. Ann Intern Med 2001;135(5):313-321.

20. Vaupel JW. Biodemography of human ageing. Nature 2010;464(7288):536-542.
21. Bootsma-van der Wiel A, Van Exel E, De Craen AJ et al. A high response is not essential to prevent selection bias: results from the Leiden 85-plus study. J Clin Epidemiol 2002;55(11):1119-1125.
22. Heeren TJ, Lagaay AM, von Beek WC, Rooymans HG, Hijmans W. Reference values for the Mini-Mental State Examination (MMSE) in octo- and nonagenarians. J Am Geriatr Soc 1990;38(10):1093-1096.
23. Sheikh J, Yesavage J. Geriatric Depression Scale (GDS): Recent evidence and development of a shorter version. In: Brink T, editor. Clinical Gerontology: A guide to assessment and Intervention. New York: The Haworth Press; 1986:165-173.
24. De Craen AJ, Heeren TJ, Gussekloo J. Accuracy of the 15-item geriatric depression scale (GDS-15) in a community sample of the oldest old. Int J Geriatr Psychiatry 2003;18(1):63-66.
25. Kempen GI, Miedema I, Ormel J, Molenaar W. The assessment of disability with the Groningen Activity Restriction Scale. Conceptual framework and psychometric properties. Soc Sci Med 1996;43(11):1601-1610.
26. Kempen G, Doeglas T, Suurmeijer. Groningen Activities Restriction Scale (GARS): een handleiding. 2 ed. Groningen: UMCG/Rijksuniversiteit Groningen, Research institute SHARE; 2012.
27. Bootsma-van der Wiel A, Gussekloo J, De Craen AJ et al. Disability in the oldest old: "can do" or "do do"? J Am Geriatr Soc 2001;49(7):909-914.
28. Aalen OO, Johansen S. Empirical Transition Matrix for Nonhomogeneous Markov-Chains Based on Censored Observations. Scandinavian Journal of Statistics 1978;5(3):141-150.
29. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Stat Med 2007;26(11):2389-2430.
30. de Wreede LC, Fiocco M, Putter H. The mstate package for estimation and prediction in non- and semi-parametric multi-state and competing risks models. Comput Methods Programs Biomed 2010;99(3):261-274.
31. R Development Core Team. A language and environment for Statistical Computing. Vienna, Austria: 2006.
32. McCusker J, Kakuma R, Abrahamowicz M. Predictors of functional decline in hospitalized elderly patients: a systematic review. J Gerontol A Biol Sci Med Sci 2002;57(9):M569-M577.
33. Mor V, Wilcox V, Rakowski W, Hiris J. Functional transitions among the elderly: patterns, predictors, and related hospital use. Am J Public Health 1994;84(8):1274-1280.
34. Oksuzyan A, Juel K, Vaupel JW, Christensen K. Men: good health and high mortality. Sex differences in health and aging. Aging Clin Exp Res 2008;20(2):91-102.
35. Bootsma-van der Wiel A, Gussekloo J, De Craen AJ, Van Exel E, Bloem BR, Westendorp RG. Common chronic diseases and general impairments as determinants of walking disability in the oldest-old population. J Am Geriatr Soc 2002;50(8):1405-1410.
36. Wang L, van BG, Kukull WB, Larson EB. Predictors of functional change: a longitudinal study of nondemented people aged 65 and older. J Am Geriatr Soc 2002;50(9):1525-1534.
37. Boorsma M, Joling K, Dussel M et al. The incidence of depression and its risk factors in Dutch nursing homes and residential care homes. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry 2012;20(11):932-942.
38. Barry LC, Soulos PR, Murphy TE, Kasl SV, Gill TM. Association between indicators of disability burden and subsequent depression among older persons. J Gerontol A Biol Sci Med Sci 2013;68(3):286-292.
39. Habicht DW, Witham MD, McMurdo ME. The under-representation of older people in clinical trials: barriers and potential solutions. J Nutr Health Aging 2008;12(3):194-196.

40. de Boer MJ, Ottervanger JP, Suryapranata H et al. Old age and outcome after primary angioplasty for acute myocardial infarction. J Am Geriatr Soc 2010;58(5):867-872.
41. Fracheboud J, Groenewoud JH, Boer R et al. Seventy-five years is an appropriate upper age limit for population-based mammography screening. Int J Cancer 2006;118(8):2020-2025.

Appendix table 3. The prevalence of disability on the individual BADL- and IADL items of the GARS at age 85 (n=597)

Item	total population	no disability	IADL-disability*	BADL-disability*
	n=597	n=143	n=299	n=155
BADL: unable to				
1. dress yourself	103 (17.3)	0	0	103 (66.5)
2. get in and out of bed	53 (8.9)	0	0	53 (34.2)
3. stand up from sitting in a chair	53 (8.9)	0.	0	53 (54.2)
4. wash face and hands	45 (7.5)	0	0	45 (29.0)
5. wash and dry whole body	124 (20.8)	0	0	124 (80.0)
6. go to the toilet	60 (10.1)	0	0	60 (38.7)
7. eat and drink	21 (3.5)	0	0	21 (13.5)
8. get around in the house	67 (11.2)	0	0	67 (43.2)
12. prepare breakfast	64 (10.7)	0	0	64 (41.3)
IADL: unable to				
9. go up and down the stairs	225 (37.7)	0	89 (29.8)	136 (87.7)
10. walk outdoors	171 (28.6)	0	50 (16.7)	121 (78.1)
11. take care of your feet and toenails	340 (57.0)	0	195 (65.2)	145 (93.5)
13. prepare dinner	209 (35.0)	0	80 (26.8)	129 (83.2)
14. light household activities	127 (21.3)	0	28 (9.4)	99 (63.9)
15. heavy household activities	350 (58.6)	0	200 (66.9)	150 (96.8)
16. wash and iron clothes	223 (37.4)	0	94 (31.4)	129 (83.2)
17. make the beds	207 (34.7)	0	80 (26.8)	127 (81.9)
18. groceries	231 (38.7)	0	105 (35.1)	126 (81.3)

Data represent numbers (%)

*Disability in BADL or IADL was considered present when a participant responded 'Cannot or only with help from others' on any BADL or IADL item, respectively



3

PREDICTIVE VALUE OF A PROFILE OF ROUTINE BLOOD MEASUREMENTS ON MORTALITY IN OLDER PERSONS IN THE GENERAL POPULATION: THE LEIDEN 85-PLUS STUDY

Anne H. van Houwelingen, Wendy P.J. den Elzen, Simon P. Mooijaart, Margot Heijmans, Jeanet W. Blom, Anton J.M. de Craen and Jacobijn Gussekloo

PLoS One. 2013;8(3):e58050. doi: 10.1371/journal.pone.0058050. Epub 2013 Mar 4

ABSTRACT

Background

Various questionnaires and performance tests predict mortality in older people. However, most are heterogeneous, laborious and a validated consensus index is not available yet. Since most older people are regularly monitored by laboratory tests, we compared the predictive value of a profile of seven routine laboratory measurements on mortality in older persons in the general population with other predictors of mortality; gait speed and disability in instrumental activities of daily living (IADL).

Methods and findings

Within the Leiden 85-plus Study, a prospective population-based study, we followed 562 participants aged 85 years for mortality over five years. At baseline (age 85 years) high-density lipoprotein cholesterol, albumin, alanine transaminase, hemoglobin, creatinin clearance, C-reactive protein and homocysteine were measured. Participants were stratified based on their number of laboratory abnormalities (0, 1, 2-4 and 5-7). The predictive capacity was compared with gait speed (6-meter walking test) and disability in IADL (Groningen Activity Restriction Scale) by C-statistics.

At baseline, 418 (74%) 85-year old participants had at least one laboratory abnormality. All-cause mortality risk increased with increasing number of laboratory abnormalities to a hazard ratio of 5.64 [95% CI 3.49-9.12] for those with 5-7 laboratory abnormalities ($p<0.001$) compared to those without abnormalities. The c-statistic was 0.66 [95% CI 0.59-0.69], similar to that of gait speed and disability in IADL.

Conclusions

In the general population of oldest old, the number of abnormalities in seven routine laboratory measurements predicts five-year mortality as accurately as gait speed and IADL disability.

INTRODUCTION

Prognostic information about life expectancy in older people is important in clinical decision-making because this population is very heterogeneous. Whereas for vital older people usual care is recommended, older people with a limited life expectancy may benefit from integrated, pro-active care[1]. In addition, although older people with a better life expectancy may benefit from cancer screening or advanced medical techniques[2], it is questionable whether older people with a higher mortality risk should be exposed to such invasive tests and/or treatments.

Various prognostic indices are available to predict prognosis in older people[3]. Self-reported questionnaires and performance tests are often used to identify older people at risk for mortality[4-6]. However, these instruments are heterogeneous and a consensus index is not yet available[4-6]. Moreover, the application of self-reported questionnaires and performance tests in the general population is laborious and time consuming. Arguably, health care for older people in general could be improved by the development of a robust prognostic tool that is easy to use, inexpensive, fast, and not dependent on healthcare personnel.

Routine clinical laboratory measurements may provide such a clinical prognostic tool. Since most older people are regularly monitored by laboratory tests for preventive or disease-related purposes, such tests may provide valuable prognostic information about older persons. Several common abnormal laboratory results are known to be predictive of poor outcomes in older persons, such as high C-reactive protein (CRP) level[7], high homocysteine level[8], low high-density lipoprotein-cholesterol (HDL-C)[9], low albumin level[10], low alanine transaminase level[11], low hemoglobin level[12, 13], and poor kidney function (low creatinin clearance)[14]. Moreover, combining laboratory results into a laboratory prognostic index maximizes their predictive utility[15-20].

Therefore, this study examines whether and to what extent a profile of seven routine laboratory parameters can predict mortality in persons aged 85 years. In addition, the results from this profile are compared with other known predictors of mortality, i.e. gait speed[21] and disability in instrumental activities of daily living (IADL)[22].

METHODS

Study population

This study was performed within the Leiden 85-plus Study, a population-based prospective follow-up study of 85-year-old inhabitants of the city of Leiden, the Netherlands[23]. Between September 1997 and September 1999, 705 inhabitants of Leiden reached the age of 85 years and were eligible to participate in this study. No exclusion criteria

were applied. Fourteen persons died prior to enrolment and 92 refused participation; 7 persons died before blood sample collection and 30 refused blood sampling. As a result, baseline laboratory data for 562 participants (80% of the eligible patients) were available for this study.

At age 85, participants were visited at their place of residence. During these visits, participants underwent face-to-face interviews and were weighed. In addition, performance tests were done and a venous blood sample was drawn. Information on medical history was obtained from standardised interviews with the participant's general practitioner (GP) or treating elderly care physician (for participants living in a nursing home). All participants gave written informed consent for the study including the use of data from their medical records for additional analysis, following explanation of the study requirements and assurance of confidentiality and anonymity. For participants with severe cognitive impairment, written informed consent was obtained from a proxy. The Medical Ethical Committee of the Leiden University Medical Center approved the study and the informed consent procedure.

Study parameters

Laboratory profile

For each individual participant, we composed a profile of results of seven laboratory measurements: CRP, homocysteine, hemoglobin, HDL-C, alanine transaminase, albumin, and creatinin clearance. These seven laboratory abnormalities were included as markers of different physiological systems; general health status (CRP), cardiovascular status (homocysteine), hematological status (hemoglobin), fatty acid metabolism (HDL-C), liver function (alanine transaminase), nutritional status (albumin), and renal function (creatinin clearance).

Non-fasting blood plasma samples were drawn before 11 am. All samples arrived within 2 hours after the sample was drawn at the laboratory. Hemoglobin levels were then determined on the day the sample was drawn with the use of an automated clinical analyzing system (Coulter Electronics, Hialeah, Florida, USA). After centrifuging with citrate as anticoagulant, plasma samples were frozen immediately to measure concentrations of homocysteine later in one batch in frozen plasma samples with a fluorescence polarization immunoassay after reduction to the free form with an IMx analyzer (Abbott, Abott Park, IL, USA) (coefficient variation 2.2-2.5%). HDL-C, albumin, alanine transaminase, creatinin, and CRP were determined on the day the sample was drawn using the fully automated Hitachi 747 and 911 (Hitachi, Tokyo, Japan). Creatinin clearance was estimated with the Cockcroft Gault formula[24].

Since clinical cut-offs are reported to be unreliable in old age[25, 26], each parameter was ranked in sex-dependent quartiles. With univariate Cox proportional hazard models, we

determined which sex-dependent quartile (high or low) per laboratory measurement predicted the highest mortality risk. Per participant, the number of abnormal laboratory results was summed, i.e. the highest quartile of CRP and homocysteine, and the lowest quartile of hemoglobin, HDL-C, alanine transaminase, albumin, and creatinin clearance.

Scores ranged from zero laboratory abnormalities to seven laboratory abnormalities. Participants were stratified in four risk groups based on the number of abnormalities (no laboratory abnormality, 1 laboratory abnormality, 2-4 laboratory abnormalities and 5-7 laboratory abnormalities).

Gait speed

Gait speed was assessed at the participant's home with a 12-m walking test, which is described in detail elsewhere[27]. In short, the course was denoted by a tape measurement of 3 m. Participants were requested to walk 2 times back and forth along the tape as quickly as possible, from a standing start position. Use of a walking aid was allowed. Total time was measured with a stopwatch. For this study we used 6-m gait speed, which is the time an older person needed for one time back and forth along a 3 meter long tape. Gait speed was calculated using distance in meters and time in seconds (m/s) for 497 (88.4%) participants. A total of 65 participants were unable to perform this test. Since older people who are unable to walk are at highest risk, those participants were considered as having the lowest possible gait speed. Gait speed was ranked in four risk groups based on sex-dependent quartiles.

Ability in instrumental activities of daily living

Disability in Instrumental Activities of daily Living (IADL) was measured annually with the Groningen Activities Restriction Scale (GARS)[28]. The GARS assesses restrictions in competence in nine basic activities of daily living (BADL) and nine IADL items. It is a self-report questionnaire and assesses therefore if someone can do the task, not if someone actually performs the task[29]. For the present analyses, only the IADL items were included. IADL included the following tasks: doing light housework, heavy cleaning, wash and iron clothes, clean and make the bed, prepare a hot meal, climbing stairs, get around outdoors, do the groceries, and attend to feet and toenails. Questions are phrased: 'Can you fully independently,…?' Answers range from 'fully independently, without any difficulty' (1 point) to 'not fully independently with someone's help' (4 points).

A summed score for IADL was calculated ranging from 9 (indicating ability to perform all activities without assistance) to 36 (indicating disability). The summed score of all participants was ranked in sex-dependent quartiles.

Mortality

Mortality data, recorded from the start of the study until participants reached the age of 90 years, were obtained from the municipal registry. Causes of death were obtained from Statistics Netherlands (CBS), where all national death certificates are coded according to the International Classification of Diseases and Related Disorders, 10th revision. Causes of death were divided into cardiovascular causes (codes I00-I99) and non-cardiovascular causes (all codes except I00-I99)[30].

Other parameters

Information on sex, level of education and institutionalization was obtained during face-to-face interviews with participants. Level of education was measured as the highest educational degree the participant had obtained. Cognitive function was measured annually with the Mini-Mental State Examination (MMSE)[31]; scores range from 0-30 points, with lower scores indicating poorer cognitive performance. Multimorbidity was defined as the presence of one or more diseases at baseline as indicated by the participants' GP, elderly care physicians, pharmacy records and laboratory findings, and included stroke, myocardial infarction, severe cognitive impairment, diabetes mellitus, Parkinson disease, hip fracture, arthritis, obstructive lung disease, and cancer[32]. The presence of severe cognitive impairment was based on a diagnosis by the participant's treating physician or a MMSE score <19 points[33]. The presence of diabetes was based on a diagnosis by the treating physician, a non-fasting glucose level >200.0 mg/dL, or the use of anti-diabetic medication.

Statistical analysis

Baseline differences between participants in the four risk groups of the laboratory profile were compared with the Jonckheere Terpstra test (for continuous nonparametric variables) or linear by linear test (for categorical variables). Kaplan-Meier curves (including log rank tests) and Cox proportional hazard models were used for the prediction of the three models (laboratory profile, gait speed, and IADL) on mortality. Since the aim of this study was to assess the predictive performance of the laboratory profile, and not to investigate the causes of disease, no adjustments were made for potential confounders.

We assessed the performance of the different prediction models with receiver operation characteristic (ROC) curves with corresponding c-statistics (neutral value 0.50 and 95% confidence intervals (CI)), using all-cause mortality as the outcome.

As additional sensitivity analyses, stratified analyses were performed for the presence of multimorbidity at baseline.

Data were analyzed with Predictive Analytics SoftWare 17.0 for Windows. A p-value of <0.05 was considered statistically significant. The reporting of this observational study followed guidelines from the STROBE statement[34].

RESULTS

Table 1 shows the characteristics of the total study population, stratified for the four risk groups of the laboratory profile. Of the 562 participants, 373 (66.4%) were female and 102 (18.1%) were living in a home for the elderly or in a nursing home.

Table 1. Baseline characteristics of the study population at age 85 years stratified according to the number of abnormal laboratory results.

	All	Number of abnormal laboratory results at baseline				p for trend
		0	1	2-4	5-7	
	n=562	n=144	n=165	n=216	n=37	
Female	373 (66.4)	97 (67.4)	107 (64.8)	142 (65.7)	27 (73.0)	0.042
Low level of education (primary school only)	363 (64.4)	89 (61.8)	94 (57.0)	164 (71.3)	26 (70.3)	0.013
Low income <€750 monthly	284 (50.5)	65 (45.1)	75 (45.5)	124 (57.4)	20 (54.1)	0.01
Home for the elderly/nursing home	102 (18.1)	14 (9.7)	22 (13.3)	50 (23.1)	16 (43.2)	<0.01
≥1 chronic diseases*	420 (74.7)	91 (63.2)	126 (76.4)	173 (80.1)	30 (81.1)	<0.01
Mini-mental state examination score (points)	26 (22-28)	27 (24-29)	27 (24-49)	25 (19-28)	22 (17-27)	<0.01
Disability in instrumental activities of daily living score (pts)	18 (12-26)	15 (11-21)	17 (12-25)	21 (14-31)	22 (17-27)	<0.01
6-meter gait speed (m/s)	1.9 (1.5-2.8)	1.8 (1.4-2.4)	1.9 (1.5-2.6)	2.1 (1.5-3.1)	2.3 (1.8-3.8)	<0.01

Continuous data are presented as median (IQR); p for trend values were obtained by Jonckheere Terpstra tests
Categorical data are presented as number (%); p for trend values were obtained by Linear by Linear tests
*cancer, myocardial infarction, stroke, dementia, diabetes, chronic obstructive pulmonary disease, Parkinson's disease, hip fracture, arthritis

At baseline, 144 participants (26.0%) had 0 abnormal laboratory results, 165 (29.4%) had 1 abnormal laboratory result, 216 participants (38.4%) had 2, 3 or 4 abnormal laboratory results, and 37 participants (6.6%) had 5, 6 or 7 abnormal laboratory results. All combinations of laboratory abnormalities for participants with 2 or 3 abnormalities occurred in a similar frequency (data not shown).

With an increasing number of abnormal laboratory results, participants were more likely to have a low income and to live in a home for the elderly or in a nursing home. In addition, participants with an increasing number of abnormalities had more multimorbidity, more disability in IADL, lower gait speed, and lower MMSE scores (Table 1).

During the 5-year follow-up, 260/562 (46%) participants died. In the univariate analysis, participants with levels within the highest quartile of CRP and homocysteine, and within the lowest quartile of hemoglobin, HDL-C, alanine transaminase, albumin and creatinin clearance, had the highest all-cause mortality risk compared to participants within the other quartiles of these laboratory values (Table 2; all p-trend <0.005, all p for 4th quartile compared to other quartiles combined <0.005).

Table 2. Univariate all-cause mortality risks for sex-dependent quartiles of laboratory results included in the laboratory profile (n=562)

	Quartile of laboratory results				p for trend	P for 4th quartile compared to the other 3 quartiles combined
	1	2	3	4		
C-reactive protein	1 (ref)	1.10 (0.75-1.61)	1.36 (0.96-1.94)	2.11 (1.51-2.95	<0.001	<0.001
Homocysteine	1 (ref)	1.14 (0.76-1.71)	2.04 (1.40-2.60)	2.75 (1.92-3.96)	<0.001	<0.001
Hemoglobin*	1 (ref)	0.98 (0.67-1.42)	1.04 (0.72-1.48)	1.82 (1.31-2.54)	<0.001	<0.001
High density lipoprotein cholesterol*	1 (ref)	1.04 (0.72-1.50)	1.01 (0.70-1.47)	1.86 (1.33-2.60)	<0.001	<0.001
Alanine transaminase*	1 (ref)	1.00 (0.69-1.44)	0.88 (0.61-1.26)	1.72 (1.23-2.39)	0.005	0.004
Albumin *	1 (ref)	1.41 (0.94-2.19)	2.10 (1.45-3.06)	3.39 (2.33-4.95)	<0.001	<0.001
Creatinin clearance *	1 (ref)	0.96 (0.66-1.41)	1.32 (0.92-1.89)	1.85 (1.31-2.61)	<0.001	<0.001

Data represent hazard ratios and 95% confidence intervals, calculated with the univariate Cox-proportional hazard model
Laboratory results are divided into sex-dependent quartiles
25th, 50th and 75th percentile limits of laboratory results stratified for sex:
Hemoglobin: homocysteine: male 10.9-13.5-17.4 umol/L, female 10.2-12.2-15.4 umol/L
High-density lipoprotein cholesterol: male 35.5-42.5-51.7 mg/dL; female: 41.7-52.1-61.8 mg/dL
Alanine transaminase: male 11-15-20 U/L; female: 11-14-17 U/L
Albumin: male: 4.0-4.2-4.4 g/dL; female: 4.0-4.2-4.4 g/dL
Creatinin clearance: male: 39.4-47.2-53.9 ml/min; female: 36.8-43.4-50.8 ml/min
C-reactive protein: male: 2-4-8 mg/L; female: 1-4-8 mg/L
Homocysteine: 10.9-13.5-17.4 umol/L, female 10.2-12.2-15.4 umol/L
* highest to lowest quartile

Figure 1 presents the cumulative mortality curves for all-cause mortality in the four risk groups depending on the laboratory profile (panel A), gait speed (panel B) and ability in IADL (panel C). Participants with 5-7 laboratory abnormalities, participants in the lowest gait speed group, and participants with the highest disability in IADL had the highest all-cause mortality risk (all log rank tests p<0.001).

Table 3 shows all-cause and cause-specific mortality risks for participants in the four risk groups based on the laboratory profile, the 6-m gait speed and the summed IADL score. Participants with 5-7 abnormal laboratory results had the highest all-cause mortality risk, compared to participants with 0 laboratory abnormal laboratory results (hazard ratio [HR] 5.64, 95% CI 3.49-9.12) (p-trend <0.001). Per additional laboratory abnormality, the mortality risk increased 1.38-fold (HR 1.38, 95% CI 1.29-1.49) (p-trend <0.001).

Participants in the group with the lowest gait speed had the highest mortality risk (HR 4.13, 95% CI 2.83-6.03) compared to those with the highest gait speed. Participants with the most disability in IADL (i.e. highest quartile of the summed IADL score) also had the highest mortality risk (HR 4.43, 95% CI 3.07-6.42) compared to participants with the least IADL disability.

Of the 260 participants that died, 102 (39.2%) died from cardiovascular causes and 158 (60.8%) from non-cardiovascular causes. Similar associations of the laboratory profile,

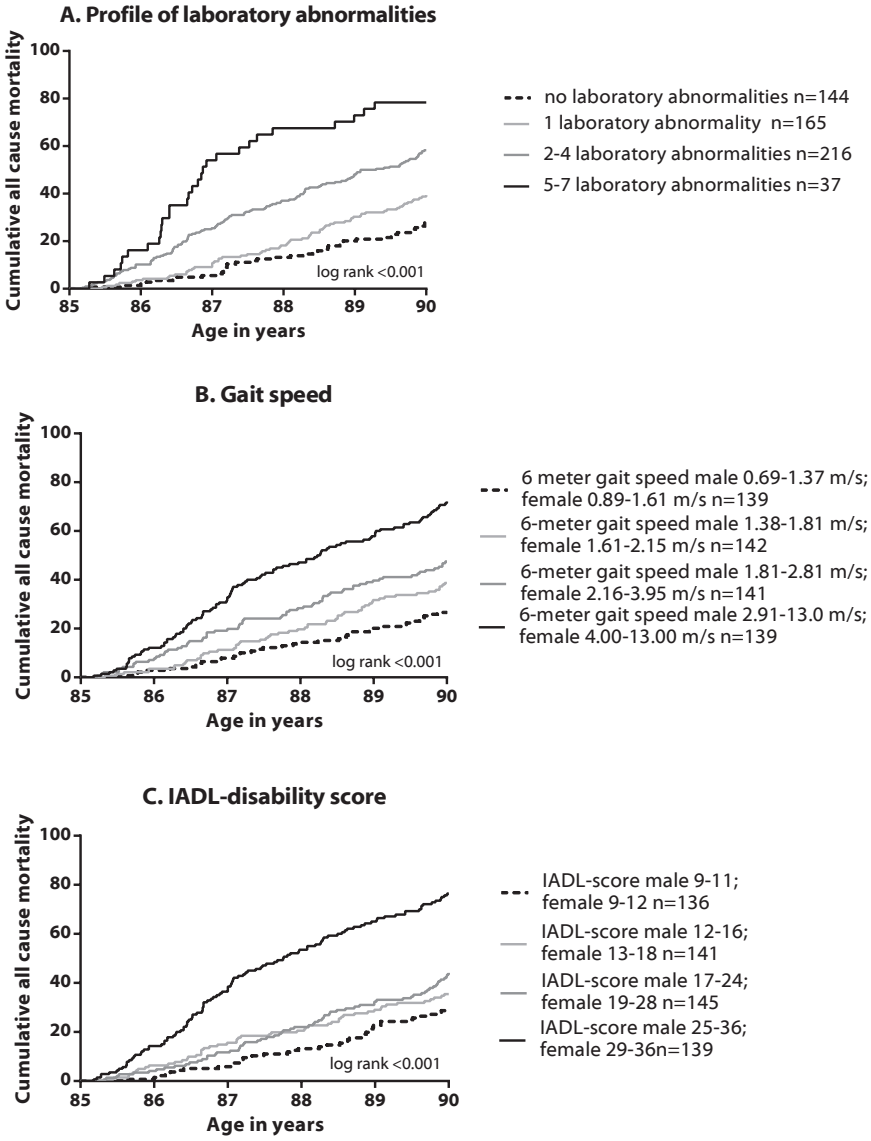


Figure 1. Kaplan Meier cumulative mortality curves for all cause mortality according to the three models. (A) laboratory profile based on sex specific quartiles of the seven included laboratory values, (B) sex specific quartiles of gait speed and (C) sex specific quartiles of instrumental activities of daily living (IADL) at age 85 years.

Table 3. All-cause and cause-specific absolute and relative mortality risk stratified for sex-dependent quartiles of the laboratory profile, IADL disability score and 6-meter gait speed.

	Risk group of predictor								
	1		2		3		4		
	Absolute risk/100 py	Hazard ratio (95% CI)	Absolute risk/100 py	Hazard ratio (95% CI)	Absolute risk/100py	Hazard ratio (95% CI)	Absolute risk/100py	Hazard ratio (95% CI)	p for trend
Laboratory profile									
All-cause mortality	6.23	1 (ref)	9.38	1.52 (1.03-2.26)	16.60	2.79 (1.96-3.99)	30.94	5.64 (3.49-9.12)	<0.001
Cardiovascular mortality	3.12	1 (ref)	2.89	0.93 (0.50-1.73)	6.32	2.08 (1.23-3.50)	14.93	5.17 (2.60-10.27)	<0.001
Non-cardiovascular mortality	3.12	1 (ref)	6.50	2.13 (1.26-3.61)	10.27	2.22 (1.59-3.09)	16.00	3.79 (2.16-6.67)	<0.001
Gait speed									
All-cause mortality	6.00	1 (ref)	9.29	1.57 (1.03-2.38)	13.74	2.13 (1.43-3.19)	22.92	4.13 (2.83-6.03)	<0.001
Cardiovascular mortality	2.43	1 (ref)	3.72	1.53 (0.80-2.96)	5.20	2.16 (1.15-4.05)	8.39	3.57 (1.96-6.52)	<0.001
Non-cardiovascular mortality	3.57	1 (ref)	5.58	1.59 (0.93-2.74)	7.24	2.11 (1.25-3.56)	14.52	4.53 (2.78-7.36)	<0.001
IADL disability									
All-cause mortality	6.46	1 (ref)	9.82	1.35 (0.89-2.05)	10.77	1.70 (1.14-2.53)	25.94	4.43 (3.07-6.42)	<0.001
Cardiovascular mortality	3.31	1 (ref)	3.10	0.94 (0.50-1.79)	3.53	1.07 (0.58-1.99)	10.28	3.28 (1.91-5.60)	<0.001
Non-cardiovascular mortality	3.15	1 (ref)	5.51	1.77 (1.00-3.12)	7.24	2.35 (1.37-4.03)	15.66	5.66 (3.38-9.46)	<0.001

Abbreviations: CI, confidence interval; IADL, instrumental activities of daily living
Gait speed and IADL disability were divided into sex-dependent quartiles
25th, 50th and 75th percentile limits of laboratory measurements stratified for sex;
Gait speed: male 1.37-1.81-2.91 m/s; female 1.61-2.15-3.95 m/s
IADL disability score: male 11-17-25 points; female 12-19-29 points

gait speed, and ability in IADL were observed for cardiovascular and non-cardiovascular mortality (Table 3).

The increased mortality risk for the risk groups based on the laboratory profile was most pronounced in older people with multimorbidity. In participants with multimorbidity the all-cause mortality risk for participants with 1 abnormality was HR 1.47 (95% CI 0.96-2.28), for participants with 2-4 abnormalities HR was 3.05 (95% CI 2.06-4.50), and for participants with 5-7 abnormalities HR was 8.71 (95% CI 5.03-15.06) (p-trend <0.001). Less pronounced results were found for participants without multimorbidity: for participants with 1 abnormality HR was 1.40 (95% CI 0.52-3.76), for 2-4 abnormalities HR was 1.90 (95% CI 0.81-4.47) and for 5-7 abnormalities HR was 2.14 (95% CI 0.55-8.28) (p-trend=0.108)

Similar associations were found when using other classifications of our profile (quartiles, tertiles, three and seven risk groups) at baseline (data not shown).

When comparing the predictive value of the laboratory profile with the models on gait speed and ability in IADL with ROC curves (Figure 2), the c-statistic for the laboratory profile was 0.66 (95% CI 0.62-0.71), for the sex-dependent quartiles of 6-m gait speed it was 0.68 (95% CI 0.63-0.73) and for sex-dependent quartiles of ability in IADL it was 0.69 (95% CI 0.64-0.73).

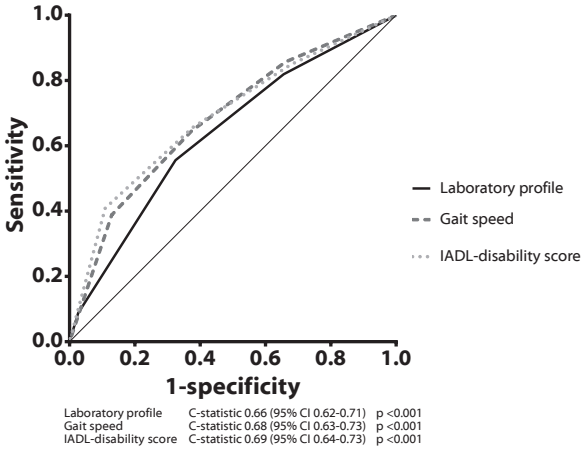


Figure 2. Performance of the three models for 5-year all-cause mortality in 562 participants aged 85 years. The three models were based on the profile of laboratory abnormalities, sex-dependent quartiles of gait speed and sex-dependent quartiles of the IADL-disability score.

DISCUSSION

In this population-based study of very old people, the number of abnormalities in a profile of seven routine laboratory measurements is a robust predictor of all-cause mortality. The predictive value of this laboratory profile was similar for cardiovascular and non-cardiovascular mortality. Moreover, mortality prediction by this laboratory profile was as accurate as models based on gait speed or IADL disability.

These results build on evidence from other studies. The present study confirms that abnormal levels of markers of physiological systems predict mortality in older individuals[19, 20, 35-38]. In contrast to these earlier studies we did not include non-laboratory markers of physiological systems (e.g. blood pressure), but selected seven common laboratory measurements reflecting dysregulation in one or more physiological systems. It is known that dysregulation in various physiological systems increases with age, and that dysregulation in multiple systems is associated with a higher mortality risk than dysregulation in one system alone[36, 37]. All of our seven routine laboratory measurements are reported to be individual predictors of poor outcome[7-14], and are individually used to guide clinical decisions and monitor disease in individual patients. This laboratory profile is easy to obtain and can be extracted from the biobanks of epidemiological studies, highlighting the potential value of this laboratory profile in older persons for research purposes.

Our study supports results from others showing that low gait speed is a powerful predictor of mortality in older people[21], and that a profile of seven routine laboratory measurements can predict mortality just as accurately. Measurement of gait speed requires training and time, and there is no uniform standard for the assessment of gait speed. Laboratory measurements are routinely determined when an older person is admitted to hospital and also in older people registered in a general practice. Therefore, this laboratory profile can be obtained with less effort than gait speed for assessing prognosis in both hospitalized and in community-dwelling older people.

Many other prognostic indices are available to predict all-cause mortality and to guide clinical decision-making[3, 39]. All these indices include chronological age, which is a powerful predictor of mortality, especially when combined with sex (c-statistic 0.75)[40]. In these models, additional predictors beyond age and sex only minimally increase discriminative power[40]. In the present study all participants were of the same age at baseline, and quartiles were sex-dependent. Although the predictive power of the laboratory profile is lower (c-statistic 0.66) compared to the earlier models, our model is valuable because it provides information beyond age and sex. In addition, it is known that biological age is more important in terms of prognosis than chronological age[41, 42]. Our profile might possibly be seen as an indicator of biological age and could, after validation in additional cohorts, be a useful tool for clinicians to assess biological age and prognosis.

The aim of this study was to investigate the predictive value of three models based on the laboratory profile, gait speed and IADL disability in the general population at large. Our study population therefore also included participants with severe cognitive impairment (MMSE <19; 90 participants). If a participant had severe cognitive impairment, a proxy was asked to attend the interview and, when necessary, to add information to the answers of the participants. Proxy information was used for IADL and BADL items of the GARS. Proxies may assess the situation of their relative either better or poorer than it actually was, resulting in non-selective misclassification of participants into incorrect IADL-quartiles. Our results may therefore be an underestimation of the true effect.

Strengths and limitations

Our study has several strengths. The Leiden 85-plus Study is a population-based prospective follow-up study with an 80% response rate and complete follow-up for mortality. These factors add to the external validity of our results. Whereas previous studies mainly focused on specific (younger) in-hospital populations, we have shown the predictive value of the laboratory profile in 85-year-old persons in the general population. Since the oldest old are the fastest growing segment of the general population, and our study is representative for this age group[23], these findings are particularly important. However, because the risk of common determinants of disease and mortality varies largely between age groups[25, 26] our results cannot automatically be extrapolated to younger populations. Another strength is that all the parameters were measured independently of adverse outcomes and without knowledge of the presence of disease. In addition, the use of quartiles of component measures instead of clinical cut-off points (that are still subject to debate), allowed us to interpret these data without prior assumptions.

A limitation of our study is the relatively small sample size. Because only 37 participants had 5, 6 or 7 abnormalities, this subgroup had to be combined. This was particularly true for older people without multimorbidity; however, trends in this group were similar to those with multimorbidity. Furthermore, we used only one baseline measurement of our laboratory profile; repeated measurements over time may provide additional information to stratify risk in this population. Another limitation is that the study was only used as a development cohort and no validation cohort was available to confirm the results. Also, since quartiles were used instead of clinical cut-off points, the use of our profile in other populations is not yet possible. Therefore, replication of these results in a validation cohort is necessary, also to establish absolute cut-offs for our index.

In conclusion, in this group of older persons, a laboratory profile of seven routine laboratory tests predicts mortality as accurately as models based on gait speed or IADL disability. This predictive study calls for confirmation in additional cohorts, as well as an in-depth analysis of the etiology and examination of its clinical use.

REFERENCES

1. Reuben DB. Medical care for the final years of life: "When you're 83, it's not going to be 20 years". JAMA 2009;302(24):2686-2694.
2. Balducci L. Aging, frailty, and chemotherapy. Cancer Control 2007;14(1):7-12.
3. Yourman LC, Lee SJ, Schonberg MA, Widera EW, Smith AK. Prognostic indices for older adults: a systematic review. JAMA 2012;307(2):182-192.
4. Vermeulen J, Neyens JC, van Rossum E, Spreeuwenberg MD, de Witte LP. Predicting ADL disability in community-dwelling elderly people using physical frailty indicators: a systematic review. BMC Geriatr 2011;11:33.
5. de Vries NM, Staal JB, van Ravensberg CD, Hobbelen JS, Olde Rikkert MG, Nijhuis-van der Sanden MW. Outcome instruments to measure frailty: a systematic review. Ageing Res Rev 2011;10(1):104-114.
6. Studenski S, Perera S, Wallace D et al. Physical performance measures in the clinical setting. J Am Geriatr Soc 2003;51(3):314-322.
7. Willems JM, Trompet S, Blauw GJ, Westendorp RG, De Craen AJ. White blood cell count and C-reactive protein are independent predictors of mortality in the oldest old. J Gerontol A Biol Sci Med Sci 2010;65(7):764-768.
8. de Ruijter W, Westendorp RG, Assendelft WJ et al. Use of Framingham risk score and new biomarkers to predict cardiovascular mortality in older people: population based observational cohort study. BMJ 2009;338:a3083.
9. Weverling-Rijnsburger AW, Jonkers IJ, Van Exel E, Gussekloo J, Westendorp RG. High-density vs low-density lipoprotein cholesterol as the risk factor for coronary artery disease and stroke in old age. Arch Intern Med 2003;163(13):1549-1554.
10. Schalk BW, Visser M, Bremmer MA, Penninx BW, Bouter LM, Deeg DJ. Change of serum albumin and risk of cardiovascular disease and all-cause mortality: Longitudinal Aging Study Amsterdam. Am J Epidemiol 2006;164(10):969-977.
11. Ford I, Mooijaart SP, Lloyd S et al. The inverse relationship between alanine aminotransferase in the normal range and adverse cardiovascular and non-cardiovascular outcomes. Int J Epidemiol 2011;40(6):1530-1538.
12. Culleton BF, Manns BJ, Zhang J, Tonelli M, Klarenbach S, Hemmelgarn BR. Impact of anemia on hospitalization and mortality in older adults. Blood 2006;107(10):3841-3846.
13. den Elzen WP, Willems JM, Westendorp RG, De Craen AJ, Assendelft WJ, Gussekloo J. Effect of anemia and comorbidity on functional status and mortality in old age: results from the Leiden 85-plus Study. CMAJ 2009;181(3-4):151-157.
14. van Bemmel T, Woittiez K, Blauw GJ et al. Prospective study of the effect of blood pressure on renal function in old age: the Leiden 85-Plus Study. J Am Soc Nephrol 2006;17(9):2561-2566.
15. Novack V, Pencina M, Zahger D et al. Routine laboratory results and thirty day and one-year mortality risk following hospitalization with acute decompensated heart failure. PLoS One 2010;5(8):e12184.
16. Bates CJ, Mansoor MA, Pentieva KD, Hamer M, Mishra GD. Biochemical risk indices, including plasma homocysteine, that prospectively predict mortality in older British people: the National Diet and Nutrition Survey of People Aged 65 Years and Over. Br J Nutr 2010;104(6):893-899.
17. May HT, Horne BD, Ronnow BS et al. Superior predictive ability for death of a basic metabolic profile risk score. Am Heart J 2009;157(5):946-954.

18. Horne BD, May HT, Muhlestein JB et al. Exceptional mortality prediction by risk scores from common laboratory tests. Am J Med 2009;122(6):550-558.
19. Giovannini S, Onder G, Liperoti R et al. Interleukin-6, C-Reactive Protein, and Tumor Necrosis Factor-Alpha as Predictors of Mortality in Frail, Community-Living Elderly Individuals. J Am Geriatr Soc 2011.
20. Pandya A, Weinstein MC, Gaziano TA. A comparative assessment of non-laboratory-based versus commonly used laboratory-based cardiovascular disease risk scores in the NHANES III population. PLoS One 2011;6(5):e20416.
21. Studenski S, Perera S, Patel K et al. Gait speed and survival in older adults. JAMA 2011;305(1):50-58.
22. Taekema DG, Gussekloo J, Westendorp RG, De Craen AJ, Maier AB. Predicting survival in oldest old people. Am J Med 2012;125(12):1188-1194.
23. Bootsma-van der Wiel A, Van Exel E, De Craen AJ et al. A high response is not essential to prevent selection bias: results from the Leiden 85-plus study. J Clin Epidemiol 2002;55(11):1119-1125.
24. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.
25. Weverling-Rijnsburger AW, Blauw GJ, Lagaay AM, Knook DL, Meinders AE, Westendorp RG. Total cholesterol and risk of mortality in the oldest old. Lancet 1997;350(9085):1119-1123.
26. van Bemmel T, Gussekloo J, Westendorp RG, Blauw GJ. In a population-based prospective study, no association between high blood pressure and mortality after age 85 years. J Hypertens 2006;24(2):287-292.
27. Bloem BR, Haan J, Lagaay AM, van Beek W, Wintzen AR, Roos RA. Investigation of gait in elderly subjects over 88 years of age. J Geriatr Psychiatry Neurol 1992;5(2):78-84.
28. Kempen GI, Miedema I, Ormel J, Molenaar W. The assessment of disability with the Groningen Activity Restriction Scale. Conceptual framework and psychometric properties. Soc Sci Med 1996;43(11):1601-1610.
29. Bootsma-van der Wiel A, Gussekloo J, De Craen AJ et al. Disability in the oldest old: "can do" or "do do"? J Am Geriatr Soc 2001;49(7):909-914.
30. World Health Organisation. International Classification of diseases and related disorders, 10th revision. 2007
31. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12(3):189-198.
32. Bootsma-van der Wiel A, De Craen AJ, Van Exel E, Macfarlane PW, Gussekloo J, Westendorp RG. Association between chronic diseases and disability in elderly subjects with low and high income: the Leiden 85-plus Study. Eur J Public Health 2005;15(5):494-497.
33. Heeren TJ, Lagaay AM, von Beek WC, Rooymans HG, Hijmans W. Reference values for the Mini-Mental State Examination (MMSE) in octo- and nonagenarians. J Am Geriatr Soc 1990;38(10):1093-1096.
34. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ 2007;335(7624):806-808.
35. Gruenewald TL, Seeman TE, Karlamangla AS, Sarkisian CA. Allostatic load and frailty in older adults. J Am Geriatr Soc 2009;57(9):1525-1531.
36. Karlamangla AS, Singer BH, McEwen BS, Rowe JW, Seeman TE. Allostatic load as a predictor of functional decline. MacArthur studies of successful aging. J Clin Epidemiol 2002;55(7):696-710.

37. Seeman TE, McEwen BS, Rowe JW, Singer BH. Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging. Proc Natl Acad Sci U S A 2001;98(8):4770-4775.
38. van Vliet P, Oleksik AM, van Heemst D, De Craen AJ, Westendorp RG. Dynamics of traditional metabolic risk factors associate with specific causes of death in old age. J Gerontol A Biol Sci Med Sci 2010;65(5):488-494.
39. Lee SJ, Lindquist K, Segal MR, Covinsky KE. Development and validation of a prognostic index for 4-year mortality in older adults. JAMA 2006;295(7):801-808.
40. De Craen AJ, Westendorp RG. Prognostic index for 4-year mortality in older adults. JAMA 2006;296(6):648-649.
41. Christensen K, Thinggaard M, McGue M et al. Perceived age as clinically useful biomarker of ageing: cohort study. BMJ 2009;339:b5262.
42. Christensen K, Iachina M, Rexbye H et al. "Looking old for your age": genetics and mortality. Epidemiology 2004;15(2):251-252.



4

CONSEQUENCES OF INTERACTION OF FUNCTIONAL, SOMATIC, MENTAL AND SOCIAL PROBLEMS IN COMMUNITY-DWELLING OLDER PEOPLE

Anne H. van Houwelingen, Wendy P.J. den Elzen, Saskia le Cessie,
Jeanet W. Blom and Jacobijn Gussekloo

PLoS One. 2015 Apr 21;10(4):e0121013. doi: 10.1371/journal.pone.0121013. eCollection 2015.

ABSTRACT

This study explores the combination of four common health problems in older people and whether problems on four domains result in an additional effect on indicators of poor health.

For this purpose, a total of 2681 participants (32% male, mean age 82 years) of the Integrated Systematic Care for Older People (ISCOPE) study were screened on the presence of health problems on four domains (functional, somatic, mental, social) with the postal ISCOPE questionnaire. Extensive interview data on health indicators were obtained at baseline and at 12-months follow-up, including disability (Groningen Activities Restriction Scale, GARS), cognitive function (Mini-Mental State Examination, MMSE), depressive symptoms (Geriatric Depression Scale-15, GDS), loneliness (loneliness scale of De Jong Gierveld), and health-related quality of life (EQ-5D). General practitioner (GP) contact time (min/year) was estimated via GP electronic medical records. Of the study population, 9% had no health problems according to the screening, 8% had problems on one domain, 27% on two, 38% on three and 18% on four domains. At baseline, the number of health domains with problems was associated with poorer scores on the GARS, the MMSE, the GDS-15, the loneliness scale, the EQ-5D and with more GP contact time ($p < 0.001$). Problems on all four domains had an additional negative effect on these health indicators (all $p_{interaction} < 0.001$). At follow-up, an increased number of domains with problems was associated with an increased decline in health indicators (all $p<0.001$) and with an additional negative effect on GP contact time of the presence of problems on all four domains ($p_{interaction} < 0.001$). We conclude that combinations of functional, somatic, mental and social problems are associated with poor health indicators in community-dwelling older people. Since problems on four domains have an additional effect on health, individuals with combined functional, somatic, mental and social problems could benefit from integrated care.

Trial registration

Netherlands Trial Register: NTR1946.

INTRODUCTION

The prevalence of many diseases and conditions increases with age. As a result, older persons often have a variety of health problems including functional, somatic, mental and social problems. These problems have all been individually associated with poor health indicators including deteriorated functional status, decreased quality of life and increased healthcare use[1-16]. Older people often have a combination of multiple health problems. However, it is unclear if these problems interact and what the consequences are of the occurrence of a combination of health problems on functioning, wellbeing and healthcare use.

Therefore, this study investigates the consequences of problems on four health domains (functional, somatic, mental and social domain) on various health indicators, and whether the problems on four domains have an interactive effect on health indicators at baseline and at 12-month follow-up.

METHODS

Study population

This study is embedded in the ISCOPE study (Integrated Systematic Care for Older PEople). ISCOPE is a cluster randomized controlled trial with randomization at general practice level. The overall aim of the ISCOPE study was to assess the efficacy of a simple structural monitoring system to detect deterioration in the functional, somatic, mental or social health of individuals aged ≥ 75 years, followed by a care plan for those people with a combination of problems on these domains. The study included 59 general practices (30 in the intervention group; 29 in the usual care group). After the general practitioners (GPs) excluded people with a life expectancy of ≤ 3 months, who were admitted to a nursing home, who were non-Dutch speaking, or who should be excluded for other relevant reasons (n=590), 11,476 older persons received an invitation to participate in the study. The ISCOPE screening questionnaire (Appendix 1) and an informed consent form were sent with this invitation. In the intervention group, the GPs received feedback about the screening questionnaire, were trained in providing pro-active integrated care for older people, and made a care plan for a randomly selected sample of 10 older persons with a combination of functional, somatic, mental or social problems. In the usual care group, the GP did not receive feedback and provided usual care.

A sample of participants who returned the screening questionnaire was visited at home by a research nurse to collect data on sociodemographic characteristics and to administer additional questionnaires on health indicators; this sample included all participants with complex problems, a random 60% of the participants with problems on 2

domains, and a random 15% of the participants with problems on 0 or 1 domain. At the 12-month follow-up, these participants were revisited to obtain additional information.

All participants gave written informed consent for the study including the use of data from their medical records for additional analysis, following explanation of the study requirements and assurance of confidentiality and anonymity. For participants with severe cognitive impairment (as judged by the research nurses) written informed consent was obtained from a proxy. The Medical Ethical Committee of the Leiden University Medical Center approved the study and the informed consent procedure.

Measurements

Identification of health domain problems at baseline

The ISCOPE screening questionnaire consists of 21 items which cover all 4 health domains (functional, somatic, mental and social domain; see Questionnaire S1)[17] . A participant was considered to have a problem on a domain, if a positive answer was given to two or more items on that domain.

Health indicators at baseline and follow-up

Disability

Disability in basic and instrumental activities of daily living (BADL and IADL) was measured with the Groningen Activities Restriction Scale (GARS)[18], a questionnaire that assesses disabilities in competence in nine BADL items and nine IADL items[19]. A sum score was calculated for the GARS, ranging from 18 (competent in all IADL and BADL activities) to 72 (unable to perform any activity without help).

Cognitive function

Cognitive function was assessed with the Mini-Mental State Examination (MMSE)[20], with scores ranging from 0-30 (=optimal).

Depressive symptoms

The presence of depressive symptoms was determined with the Geriatric Depression Scale-15 (GDS-15)[21]. The GDS-15 was restricted to people with a MMSE score of ≥ 19 since this instrument has proven unreliable for people with poor cognitive function[22].

Loneliness

Feelings of loneliness were measured with the Loneliness Scale of De Jong Gierveld[23], an 11-item scale designed for the elderly population. The maximum score was 11 points

(severe loneliness). This loneliness scale was also restricted to people with a MMSE score of ≥ 19.

Health-related Quality of Life

Health-related quality of life (HRQoL) at baseline and follow-up was evaluated with the EQ-5D[24], a standardized instrument for HRQoL.

GP contact time (during 12 months)

Data were extracted from the electronic patient records (EPR) of the participating GPs. The total number of contacts at baseline was defined as the sum of home visits and consultations in the year before the study was conducted. The total number of contacts at follow-up was defined as the sum of home visits and consultations in the year after the start of the ISCOPE-trial. To estimate the GP contact time in minutes, a GP consultation was defined to be 10 min and a home visit was defined to be 30 min (including travelling time).

Additional characteristics

Sociodemographic characteristics and chronic disease

Data on sex, living situation, marital status, educational level and chronic disease were obtained during the home interviews. Chronic diseases included diabetes, heart failure, malignancy, chronic obstructive pulmonary disease (COPD), incontinence, arthritis, osteoporosis, dizziness, lower urinary tract symptoms (LUTS), depression, anxiety, dementia, vision, deafness, fracture, stroke/transient ischemic attack (TIA) and myocardial infarction.

Statistical analysis

Descriptive statistics on sociodemographic characteristics were calculated for the total study population and stratified for the number of domains with problems. P-values for a trend for differences within these groups were obtained with the linear-by-linear chi-squared test (dichotomous data) and with linear regression analysis, with the characteristic as the dependent variable and the number of domains with problems as the independent variable (continuous data).

Linear regression analysis was used to evaluate the association between the individual domains and the number of domains with problems and the health indicators at baseline and at follow-up. In each model the number of domains with problems, as well as sex and age, were included as independent variables. For the indicators at 12 months, the score on the health indicator at baseline was added as independent variable.

We examined whether having problems on 4 domains had more effect on the health indicators than expected (from the linear model) by including an interaction variable in the model that indicated whether problems on 4 domains existed (i.e. an additive interactive effect). This variable had the value of 1 when problems on four domains existed and 0 when there were no problems on four domains. The p-value for this additional variable was indicated as $P_{interaction}$.

To investigate the relation between the number of domains with problems and dropout due to admission to a nursing home, severe (terminal) disease or death, a logistic regression analysis was performed with dropout (yes/no) as dependent variable. We also investigated whether poor cognitive function (MMSE <19) was related to dropout with the same model. The same independent variables were used as in the linear regression analysis.

A p-value <0.05 was considered to be statistically significant. Data were analyzed with the SPSS version 20.0 for Windows.

RESULTS

Study population

Of the 12,066 registered patients aged ≥75 years in the 59 general practices, 590 (4.9%) were excluded by the GP (Fig. 1). Of the remaining 11,476 patients, 7285 (63%) participated and were randomized at the level of the general practice. Of these latter persons, a random sample of 2713 was visited at home to administer the outcome measurements. Because 32 participants had missing values on one of the domains of the ISCOPE screening questionnaire and were excluded, the final study population consisted of 2681 older people.

For the GP contact time, data were available for 1473 participants because some electronic systems did not allow data extraction. Of the 2681 participants, 105 (4%) had a MMSE-score below 19 points. These participants were excluded for the GDS-15 and the Loneliness Scale of De Jong Gierveld. Table 1 summarizes the baseline characteristics of the total study population and stratified for the number of domains with problems at baseline. The median age was 82 (Interquartile range [IQR] 78-86) years and 31.7% of the study population was male.

Identification of problems at baseline

Of the study population, 243 participants (9%) had problems on no domains, 213 (8%) had problems on 1 domain, 720 had problems on 2 domains (27%), 1027 had problems on 3 domains (38%), and 478 participants had problems on all 4 domains (18%). The three combinations of problems with the highest prevalence were the combination of

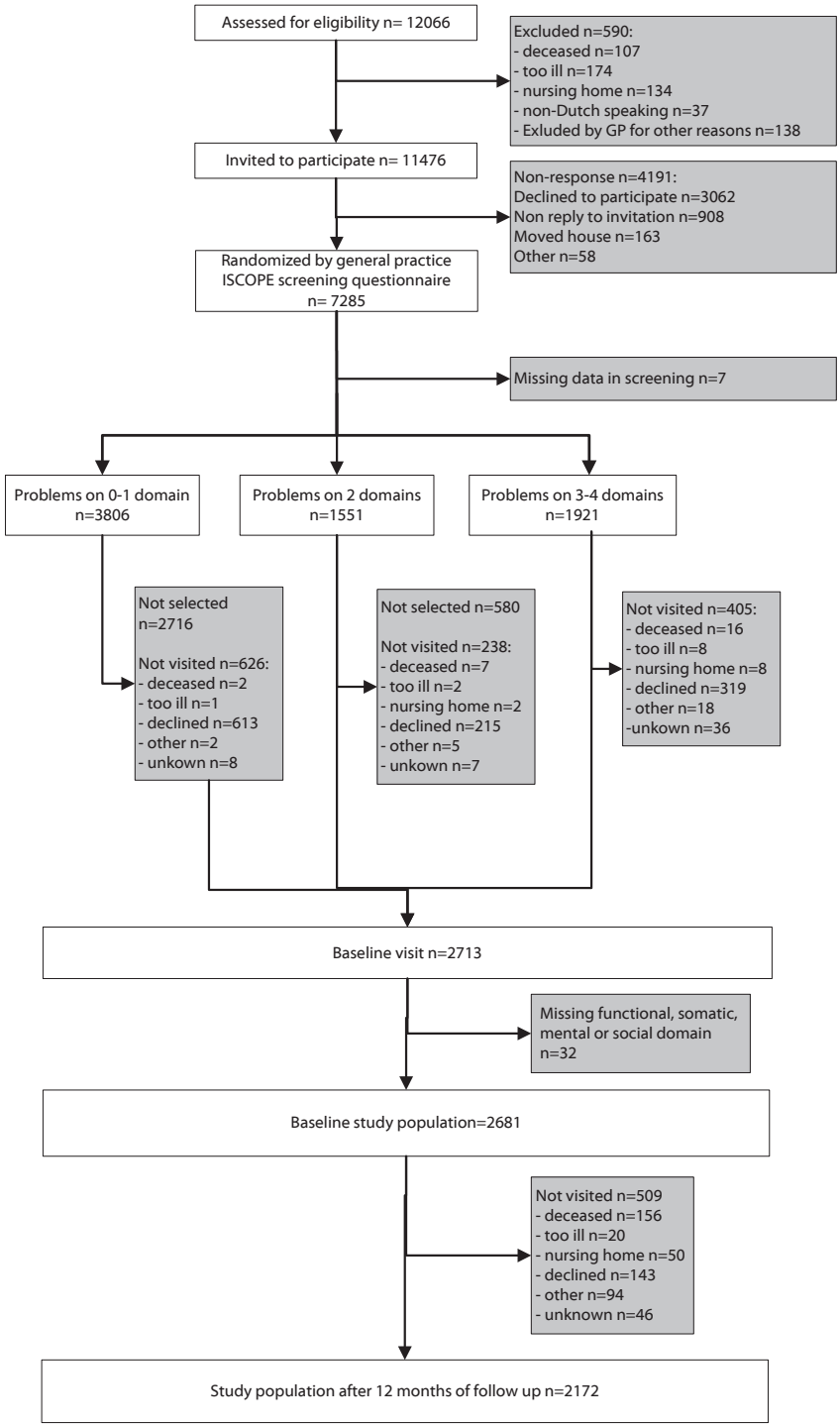


Figure 1. Flowchart of the study participants

problems on the somatic, mental and social domain (n=562, 21%), the combination of problems on all four domains (n=478, 18%) and the combination of problems on the functional, somatic and mental domain (n=341, 13%) (S1 Table). The age of the older persons increased across the increasing number of domains with problems, and the number of males decreased (Table 1; both p-trend <0.001).

A total of 1140 participants (43%) had problems on the functional domain, 2041 (76%) on the somatic domain, 1980 (74%) on the mental domain, and 1485 (55%) on the social domain. For all domains, participants with problems on any particular domain had poorer scores on health indicators (S2 Table), including higher GARS scores, higher GDS-15 scores and higher scores on the Loneliness scale, poorer EQ-5D scores and more GP contact time (all p < 0.001). Participants with problems on the functional, somatic or mental domain had lower MMSE scores (all p <0.001, S2 Table), while MMSE scores showed no difference between participants with and without problems on the social domain (p=0.68, S2 Table).

Table 1. Baseline characteristics of the total study population and stratified for the number of domains with problems

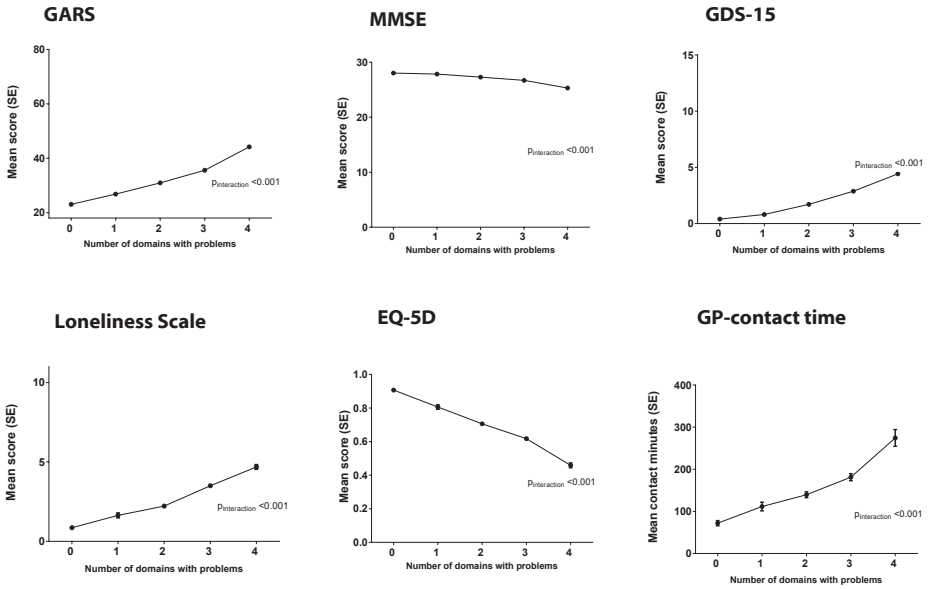
	Total study population	Number of domains with problems					
		0	1	2	3	4	
	n=2681	n=243	n=213	n=720	n=1027	n=478	p-trend
Age in years	82 (78-86)	79 (76-83)	80 (77-84)	81 (78-81)	82 (79-86)	84 (80-88)	<0.001
Male sex	850 (31.7)	118 (48.6)	79 (37.1)	225 (31.3)	325 (31.6)	103 (21.5)	<0.001
Low income (state pension only)	404 (15.1)	24 (9.9)	21 (9.9)	104 (14.4)	160 (15.6)	95 (19.9)	<0.001
Low level of education (primary school only)	967 (36.1)	65 (26.7)	69 (32.4)	248 (34.4)	374 (36.4)	211 (44.1)	<0.001
Living alone	1461 (54.5)	98 (40.3)	108 (50.7)	398 (55.3)	612 (59.6)	245 (51.3)	0.001
Widowed	1424 (53.1)	76 (31.3)	95 (44.6)	359 (49.9)	591 (57.5)	303 (63.4)	<0.001
Care home	296 (11.0)	6 (2.5)	8 (3.8)	59 (8.2)	99 (9.6)	124 (25.9)	<0.001
Number of chronic diseases*	4 (3-6)	2 (1-4)	3 (2-4)	4 (3-5)	5 (3-6)	6 (4-7)	<0.001

Data are numbers (%) or medians (Inter quartile range)
p-trend values were obtained with linear-by-linear tests (categorical data) or linear regression analysis (continuous data)
* Including self-reported diabetes, heart failure, malignancy, COPD, incontinence, arthritis, osteoporosis, dizziness, LUTS, depression, anxiety, dementia, vision, deafness, fracture, stroke/TIA, myocardial infarction.

Associations at baseline

Fig. 2 shows the association between the number of domains involved at baseline and scores on the health indicators at baseline. The number of domains with problems at baseline was associated with poor health indicators; per additional domain the GARS score was higher, the MMSE score was lower, the GDS-15 score was higher, the score on

the Loneliness Scale of De Jong Gierveld was higher, the EQ-5D score was lower, and the GP contact time was higher (all p<0.001) (Table 2). Having four domains with problems had an additional negative effect on these indicators of poor health (all p<0.05) (Table 2).



number of participants in each group: 0 domains with problems n=243, 1 domain with problems n=213, 2 domains with problems n=720, 3 domains with problems n=1027, 4 domains with problems n=478. For the GP contact time, data were available for 1473 participants, since not all electronic systems did allow data extraction (0 domains n=158, 1 domain n=123, 2 domains n=417, 3 domains n=537, 4 domains n=238).

Figure 2. Association between the number of domains with problems at baseline and scores on the health indicators.

Table 2. Association between the number of domains with problems on the health indicators at baseline (n=2681)*

	Effect of extra domain with problems at baseline		Additional effect of four domains with problems at baseline	
	β (95% CI)	p-value	β (95% CI)	p-value
GARS	3.74 (3.32;4.17)	<0.001	3.86 (2.60;5.13)	<0.001
MMSE	0.92 (0.82;1.03)	<0.001	0.78 (0.47;1.09)	<0.001
GDS-15	0.93 (0.81;1.04)	<0.001	0.40 (0.06;0.75)	0.023
Loneliness Scale of De Jong Gierveld	-0.09 (-0.11;-0.08)	<0.001	-0.06 (-0.09;-0.03)	<0.001
EQ5D	-0.40 (-0.54;0.25)	<0.001	-0.87 (-1.3;-0.44)	<0.001
GP contact time (min)‡	29 (19;40)	<0.001	49 (17;81)	<0.001

*linear regression analysis with health indicator at baseline as outcome and the number of domains with problems, as well as age and sex, as covariates

Abbreviations GARS=Groningen Activity Restriction Scale, GDS-15=Geriatric Depression Scale, MMSE=Mini-Mental State Examination, EQ-5D=Euroqol-5D, GP=general practitioner

‡ GP contact information was available for 1473 participants

Effects at follow-up

At the 12-month follow-up, 509 participants were not visited because they were deceased (n=156), too ill (n=20), admitted to a nursing home (n=50), declined further participation (n=143) or for other (n=94) or unknown reasons (n=46), resulting in a sample of 2172 participants. For GP contact time, data were available for 1422 participants at 12 months follow up, because some electronic systems did not allow data extraction.

Dropout was related to the number of domains with problems; per additional domain the odds to dropout from the study was odds ratio (OR)1.67 (95% CI 1.33-2.08; p <0.001) times higher. Having four domains with problems was not associated with an additional increased risk of dropout (OR 0.95 [95% CI 0.61-1.49], $p_{interaction}$ =0.82). The odds to dropout from the study for participants with impaired cognition (MMSE-score <19) was OR 2.54 (95% CI 1.68-3.84; p <0.001) times higher, compared to participants with MMSE score of 19 points and higher.

At the 12-month follow-up, problems on the functional domain at baseline were individually associated with poorer GARS-, MMSE-, GDS-15-, and EQ-5D- scores (linear regression analysis adjusted for the baseline score on the health indicator, age and sex, all p <0.001, S3 Table). Problems on the somatic domain and on the mental domain at baseline were individually associated with poorer scores on all these health indicators at follow up (all p <0.05, S3 Table). Problems on the social domain at baseline were associated with poorer GDS-15-, loneliness- and EQ-5D scores, and with more GP-contact time.

Table 3. Effect of the number of domains with problems on health indicators at 12-month follow-up (n=2172)*

	effect of baseline score of health indicator		effect per domain with problems at baseline		Additional effect of 4 domains with problems at baseline (interaction)	
	β (95% CI)	p-value	β (95% CI)	p-value	β (95% CI)	p-value
GARS	0.9 (0.9;0.9)	<0.001	0.7 (0.4;1.0)	<0.001	0.5 (-0.4;1.5)	0.271
MMSE	1.0 (0.9;1.0)	<0.001	-0.1 (-0.3;0.02)	0.096	-0.4 (-0.8;0.01)	0.057
GDS-15	0.6 (0.6;0.7)	<0.001	0.3 (0.2;0.4)	<0.001	0.2 (-0.1;0.5)	0.25
Loneliness Scale of De Jong Gierveld	0.6 (0.6;0.7)	<0.001	0.3 (0.2;0.4)	<0.001	-0.2 (-0.5;0.1)	0.28
EQ5D	0.4 (0.4;0.4)	<0.001	-0.06 (-0.07;-0.04)	<0.001	0.01 (-0.02;0.04)	0.69
GP-contact time (min)‡	0.7 (0.7;0.8)	<0.001	13 (3.5;22)	<0.001	52 (23;81)	<0.001

*linear regression analyses with health-indicator after 12 months as outcome and baseline score of health indicator, number of domains with problems, four domains with problems present, and age and sex as covariates.
Abbreviations GARS=Groningen Activities Restriction Scale, GDS-15=Geriatric Depression Scale, MMSE=Mini-Mental State Examination, EQ-5D=Euroqol-5D, GP=general practitioner
GP contact information was available for 1422 participants at 12 months follow up

The number of domains with problems at baseline was associated with poorer scores on the GARS, GDS-15, the Loneliness Scale of De Jong Gierveld and the EQ-5D, and with more GP contact time, adjusted for the baseline score of the health indicator, as well as age and sex (Table 3). For MMSE, there was no significant association between the number of domains with problems and the score at 12-months follow-up (p=0.096), but when participants had problems on all four domains, they showed an additional decrease in MMSE-score of -0.4 points (p=0.057). For GP contact time at 12-months follow-up, there was an additional negative effect of having 4 domains with problems on GP contact time (52 min higher [95% CI 23; 81], $P_{interaction}<0.001$).

DISCUSSION

In the present study, the number of problems on the health domains included in the ISCOPE screening questionnaire was associated with poor scores on health indicators, including disability, impaired cognition, depressive symptoms, feelings of loneliness, HRQoL and GP contact time, both at baseline and at follow-up.

Problems on 4 health domains had an interactive negative effect on disability, cognitive function, feelings of loneliness, HRQoL and GP contact time at baseline. Having problems on 4 domains was associated with an additional negative effect on GP contact time at the 12-month follow-up.

The results of the present study confirm the associations between the individual health domains and poor health indicators as reported previously[1-16]. However, to our knowledge, we are the first to show that having 4 domains with problems has additional negative consequences for older persons. It is known that multisystem physiological dysregulation has a nonlinear association with poor outcomes in older adults and that dysregulation in physiological systems increases with old age[25-27]. Moreover, paired combinations of chronic conditions have been found to have interactive effects on disability[28]. In addition, combinations of frailty with disability and multimorbidity have been proven to have interactive effects on death[29], quality of life and health care costs[30]. The present study shows that, apart from the physiological (somatic) domain and the functional domain, two other domains (mental and social) are also related to poor health and wellbeing in older individuals, and that the negative consequences increase nonlinearly when all 4 of these domains are affected. This nonlinearity might reflect the complexity that arises when several systems interact[31].

In this study, the number of items within a domain was summed and, if the result was ≥ 2, problems on a domain were considered to be present. Subsequently, we combined the domains and found that the affected number of domains was nonlinearly associated with poor health/wellbeing. Most studies are directed to one of these domains

and, if studies are directed to multiple domains, these studies add up to the number of positive items. Here, we have shown that the number of domains with problems is associated with poor health. Therefore, summing the number of positive items without taking into account the additional effect will underestimate the negative consequences for older persons with problems in multiple domains.

Strengths and limitations

A strength of the present study is the large heterogeneous study population of community- dwelling older people; this adds to the generalizability of the results. Another strength is that health indicators were measured with validated questionnaires by research nurses during home visits, increasing the reliability and the completeness of the measurements. Moreover, participants were followed for one year, which allowed studying the association between the 4 health domains and poor health indicators at 12-months follow-up.

A possible limitation is that poor MMSE-score is associated with death and nursing home admission, leading to selective dropout. This could be an explanation for the lack of association of the number of domains with MMSE-score at 12 months of follow up. Also, since the number of domains with problems at baseline was associated with an increased risk to dropout at 12 months due to death or admission to a nursing home, this group of older people might be the most vulnerable for deterioration in health. Therefore, the associations found in the present study might be an underestimation of the true effect.

Another limitation is that the studied problems on the four domains measure –to greater or lesser extent - the same constructs as some of the negative health indicators (functional domain –GARS, mental domain – MMSE and GDS-15 and social domain – Loneliness Scale of De Jong Gierveld). However, we added also the EQ-5D and GP-contact time as indicators of general health, which also show a strong association with all of the domains.

Implications

The present study shows that the number of domains with problems at baseline is associated with more disability, impaired cognition, depressive symptoms, feelings of loneliness, poorer HRQoL and more GP contact time, and that having problems on 4 domains is associated with an additional negative impact on these health indicators at baseline, and on GP contact time at follow-up. Since older people with problems on 4 domains have high care needs and poor health/wellbeing, these individuals could be candidates for integrated care. However, the provision of integrated care interventions requires careful identification of older people who will benefit from such an intervention. The method described in this study, i.e. to identify problems on 4 separate health

domains and subsequently sum the number of problems per domain, could be a promising instrument to identify older people who are likely to benefit from integrated care interventions; moreover, only a 21-item questionnaire is needed to collect all the required information. Further research is needed to develop integrated primary care interventions for older people with problems on the 4 domains as described here.

Conclusion

Having problems on four health domains is associated with the poorest scores on health indicators and has an additional negative effect on disability, cognitive function, depressive symptoms, loneliness, HRQoL, and contact time with the GP at baseline. At follow-up, the number of domains with problems is associated with poorer scores; problems on all 4 domains resulted in an additional increase in GP contact time. Problems on all 4 health domains have a nonlinear association with poor health/wellbeing, which may reflect the complexity of older individuals with problems on these domains.

REFERENCES

1. Grau L, Kovner C. Comorbidity, age, and hospital use among elderly Medicare patients. J Aging Health 1991;3(3):352-367.
2. Marengoni A, von Strauss E, Rizzuto D, Winblad B, Fratiglioni L. The impact of chronic multimorbidity and disability on functional decline and survival in elderly persons. A community-based, longitudinal study. J Intern Med 2009;265(2):288-295.
3. Glynn LG, Valderas JM, Healy P et al. The prevalence of multimorbidity in primary care and its effect on health care utilization and cost. Fam Pract 2011;28(5):516-523.
4. Fried LP, Bandeen-Roche K, Kasper JD, Guralnik JM. Association of comorbidity with disability in older women: the Women's Health and Aging Study. J Clin Epidemiol 1999;52(1):27-37.
5. Penninx BW, Geerlings SW, Deeg DJ, van Eijk JT, van Tilburg W, Beekman AT. Minor and major depression and the risk of death in older persons. Arch Gen Psychiatry 1999;56(10):889-895.
6. Beekman AT, Penninx BW, Deeg DJ, de Beurs E, Geerling SW, van Tilburg W. The impact of depression on the well-being, disability and use of services in older adults: a longitudinal perspective. Acta Psychiatr Scand 2002;105(1):20-27.
7. Lyness JM, Kim J, Tang W et al. The clinical significance of subsyndromal depression in older primary care patients. Am J Geriatr Psychiatry 2007;15(3):214-223.
8. Unutzer J, Patrick DL, Diehr P, Simon G, Grembowski D, Katon W. Quality adjusted life years in older adults with depressive symptoms and chronic medical disorders. Int Psychogeriatr 2000;12(1):15-33.
9. Van der Weele GM, Gussekloo J, De Waal MW, De Craen AJ, Van der Mast RC. Co-occurrence of depression and anxiety in elderly subjects aged 90 years and its relationship with functional status, quality of life and mortality. Int J Geriatr Psychiatry 2009;24(6):595-601.
10. Bootsma-van der Wiel A, Gussekloo J, De Craen AJ, Van Exel E, Bloem BR, Westendorp RG. Common chronic diseases and general impairments as determinants of walking disability in the oldest-old population. J Am Geriatr Soc 2002;50(8):1405-1410.
11. Perissinotto CM, Stijacic C, I, Covinsky KE. Loneliness in older persons: a predictor of functional decline and death. Arch Intern Med 2012;172(14):1078-1083.
12. Bekhet AK, Zauszniewski JA. Mental health of elders in retirement communities: is loneliness a key factor? Arch Psychiatr Nurs 2012;26(3):214-224.
13. Drageset J, Espehaug B, Kirkevold M. The impact of depression and sense of coherence on emotional and social loneliness among nursing home residents without cognitive impairment - a questionnaire survey. J Clin Nurs 2012;21(7-8):965-974.
14. Vinkers DJ, Stek ML, Gussekloo J, Van der Mast RC, Westendorp RG. Does depression in old age increase only cardiovascular mortality? The Leiden 85-plus Study. Int J Geriatr Psychiatry 2004;19(9):852-857.
15. Barry LC, Allore HG, Bruce ML, Gill TM. Longitudinal association between depressive symptoms and disability burden among older persons. J Gerontol A Biol Sci Med Sci 2009;64(12):1325-1332.
16. Hardy SE, Allore HG, Guo Z, Dubin JA, Gill TM. The effect of prior disability history on subsequent functional transitions. J Gerontol A Biol Sci Med Sci 2006;61(3):272-277.
17. Poot AJ, den Elzen WP, Blom JW, Gussekloo J. Level of satisfaction of older persons with their general practitioner and practice: role of complexity of health problems. PLoS One 2014;9(4):e94326.
18. Kempen GI, Miedema I, Ormel J, Molenaar W. The assessment of disability with the Groningen Activity Restriction Scale. Conceptual framework and psychometric properties. Soc Sci Med 1996;43(11):1601-1610.

19. Bootsma-van der Wiel A, Gussekloo J, De Craen AJ et al. Disability in the oldest old: "can do" or "do do"? J Am Geriatr Soc 2001;49(7):909-914.
20. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12(3):189-198.
21. Weeks SK, McGann PE, Michaels TK, Penninx BW. Comparing various short-form Geriatric Depression Scales leads to the GDS-5/15. J Nurs Scholarsh 2003;35(2):133-137.
22. Gussekloo J, Westendorp RG, Remarque EJ, Lagaay AM, Heeren TJ, Knook DL. Impact of mild cognitive impairment on survival in very elderly people: cohort study. BMJ 1997;315(7115):1053-1054.
23. de Jong-Gierveld J, Kamphuls F. The Development of a Rasch-Type Loneliness Scale. Applied Psychological Measurement 1985;9(3):289-299.
24. EuroQol—a new facility for the measurement of health-related quality of life. The EuroQol Group. Health Policy 1990;16(3):199-208.
25. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. J Gerontol A Biol Sci Med Sci 2004;59(3):255-263.
26. Karlamangla AS, Singer BH, McEwen BS, Rowe JW, Seeman TE. Allostatic load as a predictor of functional decline. MacArthur studies of successful aging. J Clin Epidemiol 2002;55(7):696-710.
27. Seeman TE, McEwen BS, Rowe JW, Singer BH. Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging. Proc Natl Acad Sci U S A 2001;98(8):4770-4775.
28. Tinetti ME, McAvay GJ, Chang SS et al. Contribution of multiple chronic conditions to universal health outcomes. J Am Geriatr Soc 2011;59(9):1686-1691.
29. Aarts S. Co-presence of disability and multimorbidity in health related functioning: temporary or peristent? results from a longitudinal cohort study. Multimorbidity in general practice : adverse health effects and innovative research strategies. 2012:69-81.
30. Lutomski JE, Baars MA, Boter H et al. [Frailty, disability and multi-morbidity: the relationship with quality of life and healthcare costs in elderly people]. Ned Tijdschr Geneeskd 2014;158:A7297.
31. Huyse FJ, Stiefel FC, de Jonge P. Identifiers, or "red flags," of complexity and need for integrated care. Med Clin North Am 2006;90(4):703-712.

S1 Table Prevalence of the 16 possible combinations of the domains with problems at baseline (n=2681)

Problems				
Functional	Somatic	Mental	Social	**n(%)**
-	-	-	-	243 (9)
+	-	-	-	15 (0.6)
-	+	-	-	99 (4)
-	-	+	-	63 (2)
-	-	-	+	36 (1)
+	+	-	-	139 (5)
+	-	+	-	29 (1)
+	-	-	+	14 (1)
-	+	+	-	267 (10)
-	+	-	+	86 (3)
-	-	+	+	185 (7)
+	+	+	-	341 (13)
+	-	+	+	55 (2)
+	+	-	+	69 (3)
-	+	+	+	562 (21)
+	+	+	+	478 (18)

S2 Table Baseline characteristics and scores on health indicators, for participants with and without problems on each domain (n=2681)

	Domain											
	Functional			**Somatic**			**Mental**			**Social**		
	Problems n=1140	No problems n=1541	p	Problems n=2041	No problems n=640	p	Problems n=1980	No problems n=701	p	Problems n=1485	No problems n=1196	p
Age	84 (80;89)	81 (79;85)	<0.001	83 (79;87)	81 (78;85)	<0.001	82 (79;87)	82 (78;86)	0.020	82 (79;87)	82 (78;86)	0.054
Male sex	281 (24.5)	569 (36.9)	<0.001	634 (31.1)	216 (33.8)	0.202	589 (29.7)	261 (37.2)	<0.001	411 (27.7)	439 (36.7)	<0.001
Disability (GARS)	43 (35;51)	26 (21;31)	<0.001	34 (27;44)	24 (20;30)	<0.001	33 (26;43)	28 (21;38)	<0.001	32 (25;41)	31 (24;42)	0.106
Global cognitive function (MMSE)	27 (24;28)	28 (27;29)	<0.001	28 (26;29)	28 (27;29)	<0.001	28 (26;29)	28 (26;29)	<0.001	28 (26;29)	28 (26;29)	0.675
Depressive symptoms (GDS-15)	3 (1;5)	1 (0;3)	<0.001	2 (1;4)	1 (0;2)	<0.001	2 (1;4)	0 (0;2)	<0.001	2 (1;5)	1 (0;2)	<0.001
Loneliness (Loneliness Scale of De Jong Gierveld)	3 (1;5)	2 (0;4)	<0.001	2(1;5)	1(0;4)	<0.001	3 (1;5)	1 (0;3)	<0.001	4 (2;6)	1 (0;2)	<0.001
Quality of Life (EQ-5D)	0.65 (0.25;0.78)	0.81 (0.68;0.89)	<0.001	0.69 (0.33;0.81)	0.84 (0.77;1)	<0.001	0.69 (0.36;0.81)	0.81 (0.72;1)	<0.001	0.72 (0.37;0.81)	0.81 (0.68;0.89)	<0.001
GP-contact time (minutes)	160 (70-340)	90 (40-150)	<0.001	120 (60-240)	70 (30-130)	<0.001	110 (60-220)	80 (40-170)	<0.001	110 (60-220)	90 (40-180)	<0.001

Data are numbers (%) or medians [IQR]

p-trend values were obtained with chi-square tests (categorical data) or linear regression analysis(continuous data)

GARS=Groningen Activities Restriction Scale, GDS-15=Geriatric Depression Scale, MMSE=Mini-Mental State Examination, EQ-5D=Euroqol-5D, GP=General practitioner

Individuals can have problems on more than one domain, therefore the number of participants adds up to a higher number than the study population

‡ GP contact information was available for 1473 participants

S3 Table. Association of the individual domains and the scores on health indicators at 12 months of follow-up (t12)*

	GARS		MMSE		GDS-15		Loneliness¥		EQ-5D		GP-contact time (min)	
	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p
Functional domain	3.3 (2.5;4.0)	<0.001	-0.6 (-0.8;-0.3)	<0.001	0.4 (0.2;0.6)	<0.001	-0.08 (-0.3;0.1)	0.42	-0.11 (-0.13;-0.09)	<0.001	26 (-1.9;55)	0.068
Somatic domain	1.0 (0.4;1.7)	0.003	-0.3 (-0.6;-0.06)	0.016	0.5 (0.3;0.7)	<0.001	0.4 (0.2;0.6)	<0.001	-0.09 (-0.12;-0.07)	<0.001	31 (5.7;55)	0.016
Mental domain	1.1 (0.52;1.8)	<0.001	-0.3 (-0.6;-0.01)	0.039	0.6 (0.4;0.8)	<0.001	0.5 (0.3;0.7)	<0.001	-0.09 (-0.12;0.07)	<0.001	34 (11;57)	0.004
Social domain	-0.3 (-0.6;0.5)	0.930	0.01 (-0.2;0.3)	0.962	0.3 (0.1;0.5)	<0.001	1.0 (0.8;1.1)	<0.001	-0.03 (-0.05;-0.01)	0.010	35 (15;56)	0.001

*linear regression analyses modelled on the effect of the individual domains on the score on the health-indicator at after 12 months of follow up (adjusted for age, sex and baseline score of the health indicator)

¥ Loneliness Scale of De Jong Gierveld



5

MEASURING COMPLEX PROBLEMS IN OLDER PEOPLE: CLINIMETRIC PROPERTIES OF A POSTAL SCREENING QUESTIONNAIRE

Anne H. van Houwelingen, Wendy P.J. den Elzen, Margot Heijmans,
Jacobijn Gussekloo and Jeanet W. Blom

Submitted

ABSTRACT

The identification of older persons with complex problems is receiving increasing attention. This cross-sectional study analyzes the clinimetric properties of a new self-administered postal questionnaire to identify complex problems in older persons in primary care and was embedded in the Integrated Systematic Care for Older People (ISCOPE) study. Participants filled out the ISCOPE screening questionnaire, a 21-item questionnaire measuring 4 health domains (functional, somatic, mental, social). To investigate the feasibility of the ISCOPE screening questionnaire, a non-response analysis was carried out and the proportion of patients that completed all items was calculated. Cronbach's alpha was used to assess internal consistency. Spearman's rank correlations between the questionnaire and health indicators were used to test the construct validity. Test-retest reliability was examined in a sample of 257 participants who filled out the questionnaire twice within 6 weeks. To investigate its content validity, 16 experts were invited to comment on the questionnaire.

Of the 11,479 eligible older people, 7285 (63%) participated. Of these, 7178 (98.6%) completed all 21 items of the ISCOPE screening questionnaire. Internal consistency of the 4 domains and the ISCOPE questionnaire was good for the functional (Cronbach's alpha 0.81) and social domain (0.70); the other 2 domains had poorer internal consistency (somatic domain 0.52, mental domain 0.63). All 10 hypotheses tested to assess construct validity were confirmed. The test-retest reliability of the ISCOPE questionnaire was 65-94% (i.e. substantial to good). The content validity was good: most experts considered all items to be relevant, but proposed 11 items to be added to the questionnaire.

In conclusion, the ISCOPE screening questionnaire seems an appropriate instrument to identify older people with complex problems in general practice. Generally, the feasibility, internal consistency, construct validity and test-retest reliability were reasonable. Further research should investigate the responsiveness, generalizability, and predictive validity of this questionnaire.

INTRODUCTION

The rapidly aging population in the Western world[1, 2] has important consequences for primary care, because it faces an increase in home-dwelling older persons with complex problems. The identification of older persons with complex problems, followed by geriatric assessment and long-term management, can improve the daily function of these individuals and may help prevent hospital admission and mortality[3-7]. However, the success of such programs largely depends on the identification of older persons with complex problems. Such identification may distinguish between older persons who will benefit from a pro-active approach[5, 8] and vital older persons for whom usual care is generally sufficient. Therefore, this study aimed to develop a simple measure to identify older people with complex problems who will benefit from a pro-active approach in general practice[9, 10].

The present study was embedded in the Integrated Systematic Care for Older PEople (ISCOPE) study, which investigates the (cost)-effectiveness of identification of older persons with complex problems followed by a proactive integrated care plan for these persons in general practice.

For this study we developed the ISCOPE screening questionnaire that: 1) identifies complex problems in older people in line with the definition of the Dutch College of General Practitioners, which defined complex problems as having one or more (health) problems that often interact[9, 10], 2) is suitable for older people in general practice, and 3) is discriminative: i.e. that it can be used to distinguish older persons with complex problems from vital older persons. The ISCOPE screening questionnaire consisted of 21 questions (Appendix 1) divided into 4 domains of health (i.e. functional, somatic, mental and social). Since the Dutch College of General Practitioners defines complex problems as multiple problems in multiple health domains, we used a stepped scoring system; we first summed the number of problems within a domain and subsequently added up the number of domains.

This paper reports on the development, feasibility, internal consistency, construct validity, test-retest reliability and content validity of the ISCOPE screening questionnaire.

METHODS

Development of the ISCOPE screening questionnaire

Of all items, 15 were derived from the Groningen Frailty Indicator (GFI) (items 1-4, 7-11, 14-16 and 18-20). The GFI is a short 15-item questionnaire to identify frail older people that is often used in a research or clinical setting in the Netherlands[11]. One GFI item was slightly revised: instead of 'Do you miss people around you' we included the question

'Do you miss a good friend'. Item 13 was derived from the Identification of Seniors at Risk (ISAR) tool[12], item 17 from the Geriatric Depression Scale-15 (GDS-15)[13], and item 21 was derived from the Loneliness scale of De Jong-Gierveld et al.[14]

In the ISCOPE questionnaire, the questions refer to what the participants did or how they felt in the week immediately prior to filling in the questionnaire.

Scoring

Dichotomous response options were chosen for the functional and somatic domains, and a 3-point Likert scale was chosen for the mental and social domains. A visual analog scale (VAS) score was used for two questions in the functional and somatic domains.

Problems on a domain were considered present when ≥ 2 questions on a domain were responded to positively. Complex problems were considered present when a participant had problems on ≥ 3 domains.

The score per domain was calculated when all items of the domains were completed. The number of domains was summed only when at least 3 domains were completed. The ISCOPE sum score was calculated when all items of the questionnaire were completed.

Pilot

The ISCOPE screening questionnaire was first discussed with a sample of older representatives (n=20). The questionnaire was then piloted in 3 general practices (n=556). All older people in these practices received the postal questionnaire. Of these, 369 older people gave informed consent to participate (62%); their general practitioners (GPs) were then asked to rate the complex problems of these individuals. After this pilot, the GPs received feedback on the questionnaire and were interviewed about the content of the questionnaire, its results, and any differences that emerged compared with their own impression.

Study population

The present study was embedded in the ISCOPE study which, in people aged ≥ 75 years with complex problems, compared a proactive approach by their GP with usual care (Chapter 8).

For the present study 7285 participants who filled out the ISCOPE screening questionnaire were selected; all participants provided written informed consent.

The study was approved by the Medical Ethics Committee of the Leiden University Medical Center.

Measurements

For logistical reasons, only a random sample of the study population (n=2713; 43%) was visited at home by a research nurse to obtain data on sociodemographic characteristics

and to administer additional questionnaires. All participants with complex problems were visited. In addition, a random sample of 60% of the participants with problems on 2 domains of health, and a random sample of 15% of the participants with problems on 1 or 0 domains of health, were visited.

During home visits, data on sociodemographic characteristics, multimorbidity, functional status and life satisfaction were obtained; these data were self-reported. Chronic diseases included self-reported diabetes, heart failure, malignancy, chronic obstructive pulmonary disease (COPD), incontinence, arthritis, osteoporosis, dizziness, lower urinary tract symptoms (LUTS), depression, anxiety, dementia, vision, deafness, fracture, stroke/transient ischemic attack, and myocardial infarction. A sum score of these listed diseases was calculated.

Competence in basic (BADL) and instrumental activities of daily living (IADL) was measured with the Groningen Activities Restriction Scale (GARS)[15]. The GARS is a questionnaire that assesses disabilities in competence in BADL and IADL[15, 16]. Questions were phrased: 'Can you fully independently,…?'. The items of the GARS were classified into BADL or IADL items in accordance with Bootsma-van der Wiel et al.[16]. A sum score was calculated and ranged from 18 (competent in all activities) to 72 (unable to perform any activity without help).

Global cognitive function was assessed with the Mini-Mental State Examination (MMSE) with scores ranging from 0-30 (=optimal)[17]. The Geriatric Depression Scale-15 (GDS-15) was used to assess depressive symptoms; higher scores on the GDS-15 indicate more depressive symptoms[13]. The Loneliness scale of De Jong Gierveld et al. was used to assess feelings of loneliness, with a higher score indicating more severe loneliness (range 0-11)[14]. The GDS-15 and the Loneliness scale were restricted to those individuals with an MMSE score of ≥ 19.

Life satisfaction was assessed with the Cantril ladder[18] (a VAS on perceived quality of life ranging from 1-10)

Prior to randomization the GPs received a list of all patients aged ≥ 75 years in their practices and were asked to indicate which patients were, in their opinion, 'vulnerable' individuals.

The number of GP contacts in the year before the start of the study was derived from the electronic patient records of the participants, including the number of consultations, telephone consultations and home visits.

Analyses

Feasibility

We compared responders and non-responders using patient data from one rural and one city GP practice (total of 629 patients), both of which had participated in the

ISCOPE study. Anonymous data from the electronic patient records were available for participants and non-participants. A comparison was made of sociodemographic data, diseases (ICPC codes), medication, use of care, and the GP's appraisal of vulnerability.

In addition, the proportion of participants of the total study population who completed all items of the questionnaire and completed at least 3 domains of the questionnaire, and the proportion of participants who received help with filling out the questionnaire, were calculated.

Internal consistency

The internal consistency for each domain and for the complete ISCOPE screening questionnaire was investigated. First, the internal consistency of the domains and the ISCOPE screening questionnaire was examined using Cronbach's alpha coefficient. A Cronbach's alpha coefficient > 0.7 was considered acceptable[19]. Subsequently, the average inter-item correlations were calculated, as these are independent from the scale length. We considered an average inter-item correlation of 0.20-0.70 to be satisfactory. Finally, item-rest correlations between the individual items and the sum of the remaining items of a domain were calculated.

To explore whether there was a mutual correlation between the various items of the four domains, or with items within other domains, we constructed a correlation matrix of all items and a correlation matrix of the items with problems on the individual domains.

Construct validity

Construct validity was evaluated by defining hypotheses based on previous literature[20-24] or on clinical experience. The following hypotheses were tested:

1. There is a positive correlation with age.
2. There is a positive correlation with score on the GARS.
3. There is a positive correlation with the number of contacts with the GP.
4. There is a negative correlation with the score on Cantril's ladder.
5. There is a positive correlation with the number of chronic diseases.
6. There is a positive correlation with the GP's perspective on vulnerability.
7. The correlation between the functional domain and the GARS is higher than that between the other three domains and the GARS.
8. The correlation between the somatic domain and the number of chronic diseases is higher than that between the other three domains and the number of chronic diseases.
9. The correlation between the mental domain and the GDS-15 is higher than that between the other three domains and the GDS-15.

10. The correlation between the social domain and the Loneliness scale of De Jong Gierveld et al. is higher than that between the other three domains and the Loneliness scale of De Jong Gierveld et al.

These hypotheses were tested with Spearman's correlation coefficient since the data were not normally distributed. The construct validity was considered satisfactory when ≥ 75% of our hypotheses were correct.

Test-retest reliability

Test-retest reliability refers to the reproducibility of measurements using the same instruments over time. A subgroup of the participants (n=494) from 5 general practices received the ISCOPE screening questionnaire twice (12 months after study inclusion) within a period of 2-4 weeks; this period was considered long enough to ensure that participants would not remember their first responses and short enough to ensure that the situation of the participant had not changed substantially. An item was added to the second questionnaire to assess whether participants considered themselves 'stable' during the period between the two questionnaires. Only data of participants who considered themselves to be stable were used.

Participants who received help with filling out the first or second questionnaire were also excluded; however, participants who received help with both questionnaires were included. For dichotomous response options, we used the percentage agreement and kappa statistic. For categorical response options, the intraclass correlation coefficient (ICC) and Bland and Altman plots were used. A kappa of 0.61 and an ICC of 0.70 were considered to be satisfactory[25, 26]. Mean differences between the two measurements were calculated with limits of agreement according to Bland and Altman[27].

A p-value of <0.05 was considered statistically significant. Data were analyzed with SPSS 20.0 for Windows and VassarStats website for statistical computation.

Content validity

Content validity is defined as the degree to which the content of a measurement instrument is an adequate reflection of the construct to be measured[28]. Therefore, a panel of 12 trained professionals in the geriatric field (5 GPs with special interest in elderly care, 3 elderly care physicians and 4 geriatricians) as well as 3 male and 1 female older volunteers, were asked to assess if all items were relevant and whether the questionnaire was sufficiently comprehensive. The professionals in the geriatric field were selected based on their experience in this area and familiarity with identification of complex problems in older persons. All received an email with a web link to a website, which provided them with the definition of complex problems according to the statement of the Dutch College of General Practitioners[10] and its 4 dimensions (Panel 1), and the various questions

of the ISCOPE questionnaire per domain They were asked to evaluate the relevance of each of the items per domain, to suggest items to add to a domain (only if they considered one of the domains incomplete), and to indicate if one of the original items should be replaced by one of their suggested items per domain.

Panel 1

Definitions of the construct 'Complex problems' and the four domains of the ISCOPE screening questionnaire which were presented to the expert panel

Complex problems
An older person with complex problems is someone with multiple health problems which interact. Complex problems are considered present when problems exist on three or more out of four domains; functional, somatic, mental and social. Complex problems result in deterioration in quality of life and functional decline.

Functional domain
The functional domain contains ADLs (Activities of Daily Living, i.e. basic activities including washing, dressing and undressing) and IADLs (Instrumental activities of Daily Living, i.e. household tasks including cooking, do the shopping, manage finances).

Somatic domain
The somatic domain aims to identify somatic problems including co-morbidity, poly-pharmacy and specific geriatric physical problems.

Mental domain
The mental domain identifies depressive symptoms and cognition problems

Social domain
The social domain contains loneliness and reduced social life

RESULTS

Adjustments to the ISCOPE screening questionnaire before conducting the study

The 20 older representatives that commented on the ISCOPE screening questionnaire before the study largely agreed with its contents. All of them filled out the questionnaire as though they were a participant in the study; their main comment concerned the spelling and/or formulation of some of the items. Based on these comments, the questionnaire was slightly adjusted.

This revised version of the questionnaire was then piloted in three general practices. The three GPs were asked to comment on the questionnaire. In general, they agreed that the questionnaire yielded results that were applicable in their practice, and that the

older persons with complex problems as identified with the questionnaire were eligible for integrated care.

Study population

Of the 12,066 registered persons in the 59 practices, 11,479 were eligible. The overall response rate was 63%; 7285 older persons participated in the present study. The screening questionnaire was missing for 7 persons, resulting in a study population of

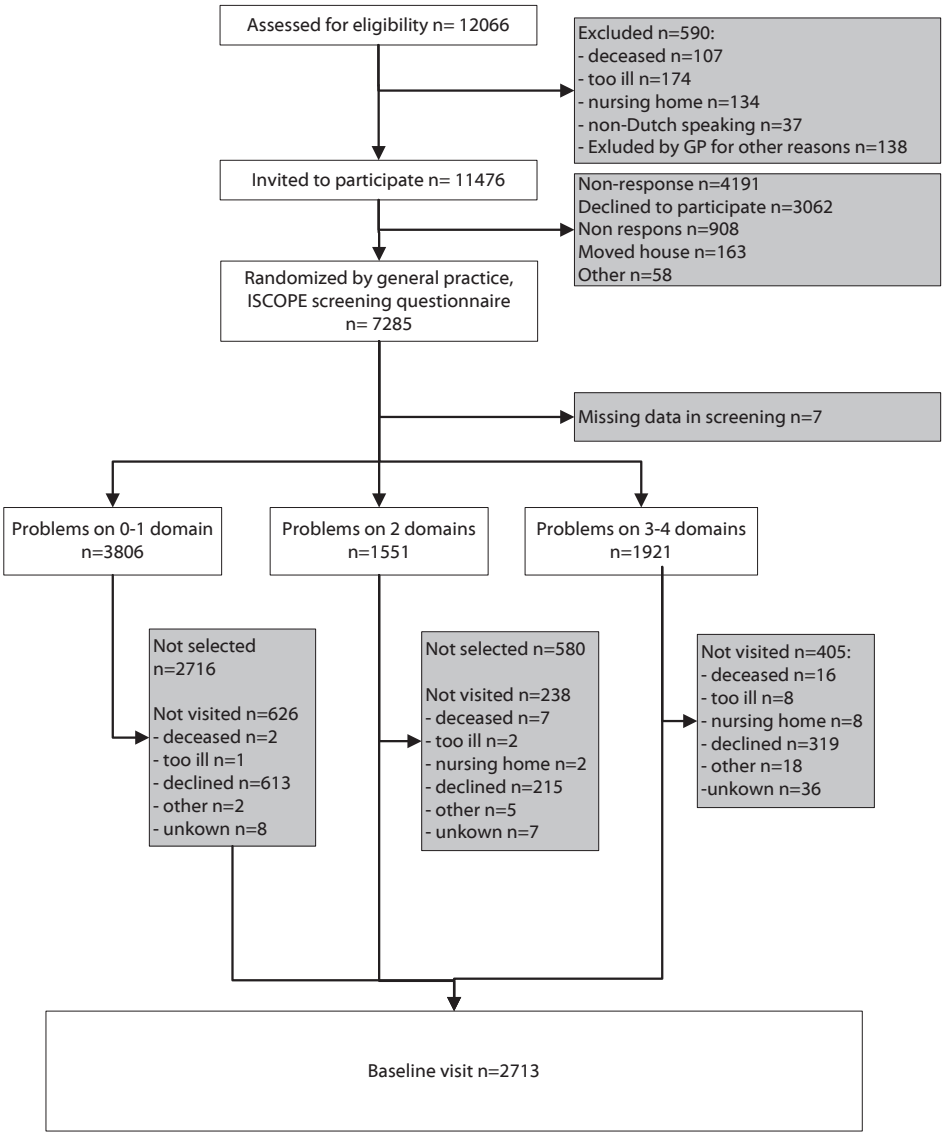


Figure 1. Flowchart of the ISCOPE study.

7278 older persons. One third of the study population (n=2713) was interviewed at home (Figure 1).

Table 1 presents the characteristics of the study population: median age was 81 (IQR 77-85) years and there were more females (61.4%) than males (38.6%). Of all participants, 26.4% had complex problems according to the ISCOPE screening questionnaire.

Table 1. Baseline characteristics of the study population (n=7278)

Age (years)	81 (77-85)
Male sex	2812 (38.6)
Number of domains with problems according to the ISCOPE questionnaire	1 (0-3)
Complex problems according to the ISCOPE questionnaire	1921 (26.4)

Data are presented as numbers (%) or median (IQR)

Feasibility

The response in the two practices for non-response analysis was 57%. Non-responders were more often women (41.9% vs 33.9%, p=0.043), were older [median 81 (IQR 78-85) years vs. 80 (77-83) years; p=0.01], were appraised more often as 'vulnerable' by the GP (25.1% vs. 15.6%; p=0.025) and received more home visits from their GP (44.6% vs 36.9%; p=0.049). In addition, cognitive decline or problems with vision were more often registered.

Of the 7285 participants included in this study, 7178 (98.6%) completed all items of the ISCOPE screening questionnaire. One third of the population (2237, 31%) was assisted by a relative (n=1395, 19%) or a research nurse (n=842, 12%). Compared with participants who did not need assistance, those with assistance were generally older, more often female, and more often had complex problems (all p <0.001). Based on the experience of the individual research nurses, it took 7-8 min to administer the questionnaire verbally. When the research nurses attended the completion of the questionnaire by the participant, the completion also took 7-8 min.

Internal consistency

The ISCOPE screening questionnaire had an internal consistency of 0.82. The internal consistency was 0.81 for the functional domain, 0.51 for the somatic domain, 0.63 for the mental domain and 0.70 for the social domain. Because the internal consistency of the somatic domain was low, we explored whether items of the somatic domain were related to other domains. The items of the somatic domain had a low correlation with the other domains (range 0.045-0.176); however, the physical fitness item correlated (range 0.40-0.47) with 3 items of the functional domain (shopping, walk outdoors and cope with general day-to-day life).

The mental domain had an internal consistency of 0.63. When we omitted the memory complaints item, the internal consistency increased to 0.69.

The average inter-item correlation was 0.372 and item-rest correlations ranged from 0.413-0.567. All domains had moderate mutual correlations: these ranged from 0.21 between the functional and social domain to 0.52 between the mental and social domain (Table 2).

Table 2. Mean scores and intercorrelations between the four domains

		N	Mean	SD	1*	2*	3*
1	Functional domain	6	0.97	1.52			
2	Somatic domain	7	1.78	1.43	0.479		
3	Mental domain	4	1.55	1.31	0.349	0.410	
4	Social domain	4	1.13	1.28	0.210	0.264	0.517

* Pearson's correlation coefficient

Construct validity

Table 3 lists all hypotheses and the corresponding correlations. All 10 hypotheses were confirmed (100%).

Test-retest reliability

Participants from 5 general practices (n=494) were invited for a test-retest analysis. We excluded participants who refused to fill out the second questionnaire (n=130), participants for whom the second questionnaire was missing (n=5), participants who reported a change (n=66), and participants who filled out the two questionnaires in two different ways (i.e. with and without assistance) (n=36). This resulted in a study population of 257 participants (52%) for the test-retest analysis. Table 4 presents the results of the first and second ISCOPE questionnaire with a median time interval between the two tests of 6 (IQR 5-7) weeks. The unadjusted agreement percentage of complex problems was 91% with a kappa of 0.71. The median number of domains with problems was the same during the first and second measurement (median 1 domain, interquartile range (IQR) 0-2 for both measurements). The agreement for the number of domains with problems was 0.76 (linear weighted kappa).

The functional domain had the highest test-retest reliability (unadjusted agreement 94%, kappa 0.81). Agreement and kappa for the other domains was 84% and 0.68 for the mental domain, 86% and 0.71 for the somatic domain, and 88% and 0.69 for the social domain, respectively. For the individual items, agreement ranged from 84-99%. Kappas ranged from 0.42 to 0.85. The falls item and the close connection item had moderate kappas, but relatively high percentages of agreement, because of the low prevalence[29].

Table 3. Construct validity of the ISCOPE screening questionnaire

	Hypothesis*	n	Spearman's correlation coefficient	p-value
	Presence of complex problems			
1	Age	2713	0.172	<0.001
2	Disability	2713	0.422	<0.001
3	Health care use	2713	0.196	<0.001
4	Life satisfaction	2713	-0.290	<0.001
5	Diseases	2713	0.324	<0.001
6	GP's perspective	2534	0.212	<0.001
	Domains			
7	Functional domain			
	Functional domain - GARS	2683	0.668	<0.001
	Somatic domain - GARS	2676	0.393	<0.001
	Mental domain - GARS	2679	0.160	<0.001
	Social domain - GARS	2683	0.046	0.023
8	Somatic domain			
	Somatic domain - number of chronic diseases	2709	0.369	<0.001
	Functional domain - number of chronic diseases	2702	0.254	<0.001
	Mental domain - number of chronic diseases	2705	0.266	<0.001
	Social domain - number of chronic diseases	2708	0.144	<0.001
9	Mental domain			
	Psychological domain – GDS-15	2548	0.368	<0.001
	Functional domain – GDS-15	2544	0.288	<0.001
	Somatic domain – GDS-15	2544	0.254	<0.001
	Social domain – GDS-15	2544	0.277	<0.001
10	Social domain			
	Social domain - Loneliness Scale	2542	0.535	<0.001
	Functional domain - Loneliness Scale	2542	0.071	<0.001
	Somatic domain - Loneliness Scale	2538	0.124	<0.001
	Mental domain - Loneliness Scale	2538	0.270	<0.001

GFI=Groningen Frailty Indicator, GARS=Groningen Activities Restriction scale, GDS-15=Geriatric Depression Scale-15

10 hypotheses were tested:

1. There is a positive correlation with age
2. There is a positive correlation with score on the GARS
3. There is a positive correlation with the number of contacts with the GP
4. There is a negative correlation with score on Cantril's ladder
5. There is a positive correlation with the number of chronic diseases
6. There is a positive correlation with GP's perspective on vulnerability
7. The correlation between the functional domain and the GARS is higher than the correlation between the other three domains and the GARS
8. The correlation between the somatic domain and the number of chronic diseases is higher than the correlation between the other three domains and the number of chronic diseases
9. The correlation between the mental domain and the GDS-15 is higher than the correlation between the other three domains and the GDS-15
10. The correlation between the social domain and the Loneliness scale of De Jong Gierveld et al. is higher than the correlation between the other three domains and the Loneliness scale of De Jong Gierveld et al.

Table 4. Test-retest reliability of respondents of the ISCOPE screening questionnaire (n=257)

	Time 1	Time 2	Agreement	(weighted) Kappa or ICC
	n (%)	n (%)		
Age*	81 (79-85)			
Male sex	114 (44.4)			
Functional domain	48 (18.7)	51 (19.6)	94	0.812
shopping	38 (14.8)	42 (16.3)	96	0.852
walk outdoors	27 (10.5)	33 (12.8)	95	0.736
dress and undress	9 (3.5)	14 (5.4)	98	0.773
go to the toilet	1 (0.4)	2 (0.8)	99.6	0.665
manage finances	37 (14.4)	40 (15.6)	91	0.649
cope with your general day to day life	67 (26.1)	61 (23.7)	87	0.647
Somatic domain	112 (43.6)	112 (43.6)	86	0.714
physical fitness	79 (30.7)	84 (32.7)	89	0.740
vision	40 (15.6)	39 (15.2)	94	0.776
hearing	64 (24.9)	57 (22.2)	90	0.730
unintentional weight loss	11 (4.3)	7 (2.7)	98	0.770
$\geq$ 4 different kinds of medicines	147 (57.2)	153 (59.9)	92	0.840
falls	18 (7.0)	25 (9.7)	91	0.418
hospital admission	29 (11.3)	25 (9.7)	97	0.835
Mental domain	104 (40.5)	106 (41.2)	84	0.678
memory complaints	125 (48.6)	120 (46.7)	86	0.727
sad or depressed	104 (40.5)	100 (38.9)	85	0.691
nervous or anxious	74 (28.8)	74 (28.9)	82	0.564
worthless	59 (23.0)	55 (21.4)	84	0.527
Social domain	74 (28.8)	70 (27.2)	88	0.691
emptiness	105 (40.9)	101 (39.3)	84	0.660
lack of a close friend	76 (29.6)	73 (28.4)	85	0.631
left alone	54 (21.0)	48 (18.7)	88	0.633
close connection to people	23 (8.9)	27 (10.5)	90	0.424
Number of domains with problems*	1 (0-2)	1 (0-2)	66	0.761
Total score on ISCOPE questionnaire*	4 (2-7)	4 (2-7)	36	0.918
Complex problems	46 (17.9)	53 (20.6)	91	0.713

* data are presented as median (IQR)

During both the first and second measurements, the median score for the ISCOPE sum score remained the same and the reliability was high (ICC 0.92 [95% CI 0.90-0.94]). Figure 2 shows the differences between the two measurements of the ISCOPE sum score against their means[27].

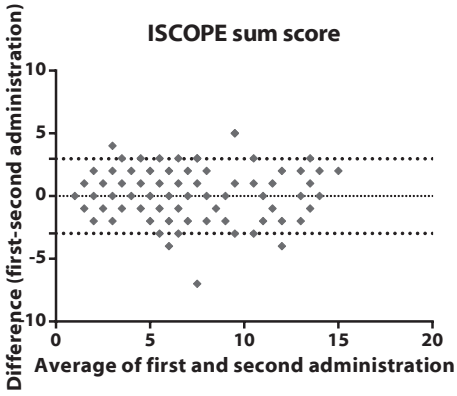


Figure 2. Bland and Altman plots of the ISCOPE sum score on the ISCOPE screening questionnaire during the first and the second administration (n=257).

Content validity

Panel 1 presents the definitions of the construct complex problems and the 4 domains which were presented to the experts. Most experts considered the items of the ISCOPE screening questionnaire to be relevant for the domain to be measured (Table 5). However, the experts did not find the questionnaire totally comprehensive and suggested to add 30 items (7 to the functional domain, 13 to the somatic domain, 3 to the mental domain, and 7 to the social domain). The experts indicated that 11 of the original items could be replaced. Appendix 2 shows the items that the experts suggested should be added and those that they recommended to be replaced.

Table 5. Content validity of the ISCOPE screening questionnaire according to the 16 experts.

	All questions relevant	Domain complete	Replace items
	n/16	n/16	n/16
Functional domain	13	2	6
Somatic domain	14	4	4
Mental domain	14	8	3
Social domain	14	7	7

DISCUSSION

The aim of this study was to describe the clinimetric properties of the ISCOPE screening questionnaire, which aims to identify community-dwelling older people with complex problems by postal screening. Complex problems were defined as a combination of problems on 3 or 4 health domains (functional, somatic, mental and social) of the ISCOPE screening questionnaire. Over 25% of our population was classified as having complex problems. After investigating the feasibility, internal consistency, construct validity test-retest reliability and content validity of the questionnaire, all these clinimetric properties proved to be reasonable.

The items within the health domains were based on a clinical understanding of the problems belonging to each domain. Therefore, the domains are not totally comprehensive and this explains the slightly low internal consistencies. This was confirmed by the comments of the experts about the content validity of the questionnaire, i.e. they considered most of the items to be relevant, but suggested adding 11 items that they considered to be missing.

With regard to test-retest reliability, the results show strong to complete agreement between the first and second questionnaire.

Strengths and limitations

The present study has some major strengths. First, it was embedded in the ISCOPE study which is a pragmatic randomized trial with few exclusion criteria. This enabled us to include a very heterogeneous community-dwelling older population, which supports the generalizability of the results. Another strength is the stepped scoring system (i.e. summing the number of problems within a domain and subsequently adding up the number of domains), instead of summing the number of positive items, which is a common scoring system for other instruments, such as the GFI. Our system better reflects the combination of health problems that determine complex problems in older people and is in line with the statement of the Dutch College of General Practitioners on complex problems in older people[10]. As far as we know, we are the first to use such scoring system to identify older people with complex problems.

A limitation of this study is that, for logistical reasons, the expert consultations (and their ideas) about the ISCOPE screening questionnaire could not take place before the measurements were made and, therefore, could not be included in this study. However, the experts' suggestions will be used to revise the ISCOPE screening questionnaire for further research; then, this later revised version will be tested against the unrevised version of the ISCOPE screening questionnaire.

The moderate response rate may limit the feasibility of our questionnaire for general practice. However, this was measured in a research setting with an intervention and

home visits following the questionnaire, and could be higher in a 'real life' situation. It is reported that older individuals who do not respond tend to have more complex problems than the respondents[30, 31]. In our study, we found that non-responders and responders were largely similar, but non-responders more often had problems with vision and cognitive impairment, were more often appraised as 'vulnerable' by their GP and received more home visits. This indicates that these older people may indeed have more complex problems than responders.

Of the responders, about a third received help with completing the questionnaire. Most of these older persons were assisted by a relative, which will probably be the case when the questionnaire is implemented in general practice; the remainder was assisted by a research nurse. Although this resulted in very few missing values, the question arises whether a GP (or practice staff) will have sufficient time to perform such a follow-up in general practice.

Conclusion

The ISCOPE screening questionnaire is a promising self-report instrument to identify older individuals with complex problems in the general population. However, additional studies on the responsiveness, generalizability, construct and predictive validity of the ISCOPE screening questionnaire are needed. Moreover, the ISCOPE screening questionnaire may be further improved based on the suggestions of the experts as described in this study. In addition, since this questionnaire was developed to identify older persons with complex problems who were likely to benefit most from integrated geriatric care, we need to investigate whether older persons with complex problems (as identified with this questionnaire) indeed show poor scores on health outcomes and whether they actually benefit most from integrated geriatric care.

REFERENCES

1. Christensen K, Doblhammer G, Rau R, Vaupel JW. Ageing populations: the challenges ahead. Lancet 2009;374(9696):1196-1208.
2. Lutz W, Sanderson W, Scherbov S. The coming acceleration of global population ageing. Nature 2008;451(7179):716-719.
3. Stuck AE, Siu AL, Wieland GD, Adams J, Rubenstein LZ. Comprehensive geriatric assessment: a meta-analysis of controlled trials. Lancet 1993;342(8878):1032-1036.
4. Stuck AE, Aronow HU, Steiner A et al. A trial of annual in-home comprehensive geriatric assessments for elderly people living in the community. N Engl J Med 1995;333(18):1184-1189.
5. Boyd CM, Boult C, Shadmi E et al. Guided care for multimorbid older adults. Gerontologist 2007;47(5):697-704.
6. Melis RJ, van Eijken MI, Teerenstra S et al. A randomized study of a multidisciplinary program to intervene on geriatric syndromes in vulnerable older people who live at home (Dutch EASYcare Study). J Gerontol A Biol Sci Med Sci 2008;63(3):283-290.
7. Monteserin R, Brotons C, Moral I et al. Effectiveness of a geriatric intervention in primary care: a randomized clinical trial. Fam Pract 2010;27(3):239-245.
8. Reuben DB. Medical care for the final years of life: "When you're 83, it's not going to be 20 years". JAMA 2009;302(24):2686-2694.
9. https://www.nhg.org/dutch-college-general-practitioners . 4-9-2013.
10. NHG-standpunt Toekomstvisie Huisartsenzorg. Huisartsgeneeskunde voor ouderen. NHG, 2007. 31-5-2007.
11. Steverink S, Slaets JP, Schuurmans H, Van Lis M. Measuring frailty: developing and testing the GFI (Groningen frailty Indicator). Gerontologist 2001;41:236-237.
12. McCusker J, Bellavance F, Cardin S, Trepanier S. Screening for geriatric problems in the emergency department: reliability and validity. Identification of Seniors at Risk (ISAR) Steering Committee. Acad Emerg Med 1998;5(9):883-893.
13. Weeks SK, McGann PE, Michaels TK, Penninx BW. Comparing various short-form Geriatric Depression Scales leads to the GDS-5/15. J Nurs Scholarsh 2003;35(2):133-137.
14. de Jong-Gierveld J, Kamphuls F. The Development of a Rasch-Type Loneliness Scale. Applied Psychological Measurement 1985;9(3):289-299.
15. Kempen GI, Miedema I, Ormel J, Molenaar W. The assessment of disability with the Groningen Activity Restriction Scale. Conceptual framework and psychometric properties. Soc Sci Med 1996;43(11):1601-1610.
16. Bootsma-van der Wiel A, Gussekloo J, De Craen AJ et al. Disability in the oldest old: "can do" or "do do"? J Am Geriatr Soc 2001;49(7):909-914.
17. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12(3):189-198.
18. Cantril H. The pattern of human concern. Rutgers University Press; 1965.
19. Bland JM, Altman DG. Cronbach's alpha. BMJ 1997;314(7080):572.
20. Alessi CA, Josephson KR, Harker JO, Pietruszka FM, Hoyl MT, Rubenstein LZ. The yield, reliability, and validity of a postal survey for screening community-dwelling older people. J Am Geriatr Soc 2003;51(2):194-202.
21. De Saint-Hubert M, Schoevaerdts D, Cornette P, D'Hoore W, Boland B, Swine C. Predicting functional adverse outcomes in hospitalized older patients: a systematic review of screening tools. J Nutr Health Aging 2010;14(5):394-399.

22. Peters LL, Boter H, Buskens E, Slaets JP. Measurement Properties of the Groningen Frailty Indicator in Home-Dwelling and Institutionalized Elderly People. J Am Med Dir Assoc 2012;13(6):546-551.
23. Ravaglia G, Forti P, Lucicesare A, Pisacane N, Rietti E, Patterson C. Development of an easy prognostic score for frailty outcomes in the aged. Age Ageing 2008;37(2):161-166.
24. Grant RW, Ashburner JM, Hong CC, Chang Y, Barry MJ, Atlas SJ. Defining Patient Complexity From the Primary Care Physician's Perspective A Cohort Study. Ann of Intern Med 2011;155(12):797-804.
25. Streiner DL, Norman G.R. Health measurement scales. A practical guide to their development and use. 4ed. New York: Oxford University press; 2008.
26. Aaronson N, Alonso J, Burnam A et al. Assessing health status and quality-of-life instruments: attributes and review criteria. Qual Life Res 2002;11(3):193-205.
27. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1(8476):307-310.
28. Mokkink LB, Terwee CB, Patrick DL et al. The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study. Qual Life Res 2010;19(4):539-549.
29. Feinstein AR, Cicchetti D. High agreement but low Kappa: I. the problems of two paradoxes. J Clin Epidemiol 1990;43(6):543-549.
30. Barreto PS. Participation bias in postal surveys among older adults: the role played by self-reported health, physical functional decline and frailty. Arch Gerontol Geriatr 2012;55(3):592-598.
31. Bowns I, Challis D, Tong MS. Case finding in elderly people: validation of a postal questionnaire. Br J Gen Pract 1991;41(344):100-104.



6

COMPARISON OF THREE MEASURES TO IDENTIFY OLDER PERSONS WITH PROBLEMS ON MULTIPLE HEALTH DOMAINS IN PRIMARY CARE

Anne H. van Houwelingen, Sophie I. van Dongen,
Jacobijn Gussekloo, Jeanet W. Blom and Wendy P.J. den Elzen

Submitted

ABSTRACT

General practitioners are increasingly involved with older people with problems in multiple health domains, but validated measures designed to identify these older persons in primary care are scarce. In this cross-sectional study, we compared three measures to identify this group of older people in primary care: the GP's clinical intuition on vulnerability, the Fried frailty phenotype criteria (frailty; ≥3 frailty criteria), and the ISCOPE-screening questionnaire (complex problems; problems on 3-4 health domains).

Our study population consisted of 823 participants who participated in the Integrated Systematic Care for Older PEople (ISCOPE) study (69% women, median age 83 years). During home visits, data on indicators of health were gathered; chronic diseases, disability (GARS), depressive symptoms (GDS-15), cognitive function (MMSE), loneliness (De Jong Gierveld Loneliness Scale) and life satisfaction (Cantril's ladder).

Overall, 27% of the older persons were vulnerable according to the GP, 34% was frail according to the Fried criteria and 51% had complex problems according to the ISCOPE-screening questionnaire. Older persons identified by one of these measures had, regardless of the measure, more chronic diseases, more disability, more cognitive impairment, more depressive symptoms and poorer life satisfaction. Compared with the other measures, the Fried frailty criteria were most strongly associated with disability and the ISCOPE-screening questionnaire most strongly with loneliness. All three measures identified older people with problems in multiple health domains. Since the patterns of poorer scores on health indicators varied between the three measures, the choice of a measure should depend on the intended intervention of the GP.

INTRODUCTION

Because of the ageing population, general practitioners (GPs) are increasingly involved with older people with problems in multiple health domains, i.e. combinations of somatic, functional, mental and social problems. GPs are increasingly interested and motivated to implement proactive care interventions to prevent functional decline in these older persons[1]. Before such interventions can be accomplished, measures are needed to identify older persons with problems in multiple health domains in primary care.

There are various measures to identify these older persons[2-9], but most of these measures are seldom used in, or not validated for primary care[10]. Therefore, the aim of this paper was to investigate three measures in primary care by comparing their yield on health indicators (chronic disease, disability, cognitive functioning, depressive symptoms, feelings of loneliness and GP healthcare use). These three measures were: the clinical intuition of the GP, the Fried frailty phenotype and the ISCOPE screening questionnaire.

We selected the clinical intuition of the GP, because most GPs are intuitively aware of vulnerability in older people[10, 11]. No studies have investigated this intuition on vulnerability as a measure to identify older people for proactive care interventions in primary care.

The Fried frailty phenotype[5] was selected, because it is an internationally recognised and validated measure for frailty. Frailty describes the interrelation of multiple health domains in older people. It is unknown if the Fried frailty phenotype can be used as a measure to identify older people for proactive interventions in primary care.

The ISCOPE screening questionnaire was selected because it was developed to identify older people with complex problems in primary care. This new questionnaire is a self-report instrument that defines complex problems as facing problems in 3 or 4 health domains (i.e. functional, somatic, mental, and social)[12].

METHODS

Study population

The study population consisted of older adults aged 75 years and over who participated in the Integrated Systematic Care for Older People (ISCOPE) study. The ISCOPE study is a pragmatic cluster randomized controlled trial to investigate whether a proactive approach by the GP is effective to prevent deterioration in functional status and quality of life of older people with complex problems. Complex problems were defined as having problems in at least three of four predefined domains: functional, somatic, mental and

social and was assessed by the ISCOPE screening questionnaire (Appendix 1) (Poot et al., 2014).

The ISCOPE study population was recruited from 59 participating primary care practices (30 intervention practices, 29 control practices). All older adults aged 75 years and over enlisted in these practices were targeted (n=12,066). The GPs excluded people who were deceased, too ill, non-Dutch speaking, admitted to a nursing home, or judged unsuitable to participate (n=590). The remaining 11,476 eligible individuals were sent a written screening questionnaire. A total of 7285 older persons responded by sending in the complete screening questionnaire. Of these 7285 older persons, a random sample was visited at home. During these visits, research nurses collected additional data. Based on the outcomes of the screening questionnaire, all participants with problems on 3 or 4 domains were visited. Of the participants with problems on 0 or 1 domain, 15% was visited and of those with problems on 2 domains, 60% was visited. In total, 2713 participants were visited at home to obtain data on socio-demographic characteristics, residency, functional status and the presence of disease.

In the ISCOPE study, GPs in the intervention practices provided proactive care to older people with complex health problems. In the control practices, GPs provided usual care for older people with complex health problems.

For the present analyses, a subgroup of 823 participants was randomly selected from 22 of the 59 practices (both control- and intervention practices)[13]. Participants with complex problems according to the ISCOPE screening questionnaire were oversampled. These 823 participants received an additional questionnaire and additional measurements on handgrip strength and gait speed during the home visits.

Written informed consent was obtained from all participants, or, in case of severe cognitive impairment, from a proxy. The Medical Ethics Committee of Leiden University Medical Center approved the study.

Study parameters

Measures to identify older people with problems in multiple domains

GP's clinical intuition

Prior to randomization of their practices, GPs reviewed a list of their patients aged ≥75 years, who were eligible for the ISCOPE study and indicated which patients they considered to be vulnerable (i.e. classification into not vulnerable, possibly vulnerable, and vulnerable for certain). Individuals who were labelled vulnerable for certain by their GP were considered to be at highest risk for problems in multiple domains, these older persons were considered identified by the GP. The GPs were not provided with a specific definition of 'vulnerability'[14].

Fried frailty phenotype criteria

This phenotype classifies older people as frail if they meet ≥3 of the following criteria[5]:

- Unintentional weight loss (≥5% of body weight in the last year)
- Exhaustion (positive response to questions regarding effort required for activity)
- Weakness (decreased grip strength)
- Slow walking speed (gait speed)
- Decreased physical activity (males expending <383 kcal and females <270 kcal per week)

In the present study, we slightly modified the original Fried frailty criteria for practical reasons[15]. Unintentional weight loss was defined as the self-reported unintentional loss of ≥5 kg or 5.0% of the current weight in the previous year. We used the relevant Center for Epidemiologic Studies Depression Scale (CES-D) items to measure exhaustion[16]. Hand grip strength was measured with a Jamar hand dynamometer (Sammibs Preston Inc. Bolingbrook, IL, USA). The participant was asked to stand up and hold the dynamometer in the dominant hand with the arm parallel to the body without squeezing the arm against the body. The width of the handle was adjusted to the size of the participant's hand to ensure that the middle phalanx rested on the inner handle. After one test trial, three trials followed and the best score was used for analysis. Cut-off points were defined as (<29 kg for men and <17 kg for women)[5]. Subjects who were unable to complete the hand grip strength test were considered to have weak hand grip strength.

Research nurses assessed gait speed with a 12-m walking test. First, they denoted a 3-meter course using a tape measurement; then, participants were asked to walk back and forth as quickly as possible from a standing start position. Use of a walking aid was allowed. We considered gait speed ≤0.76 m/s to be slow[5]. Subjects who were unable to complete the gait speed test were considered to have a slow gait speed.

We based the decreased physical activity criterion on the self-reported level of physical activity. This criterion was met if a participant responded affirmatively to the question 'Do you sit more than 4 hours a day?' and additionally indicated that he/she walked or was otherwise physically active less than once a month.

ISCOPE screening questionnaire

The ISCOPE screening questionnaire (Appendix 1) is a self-report short assessment instrument that aims to identify subjects with complex problems among older people in the general population. It consists of 21 questions divided into 4 domains of health. Problems on a domain were considered present when ≥2 domain-specific questions were answered affirmatively. Complex problems were considered to be present when a participant had problems in ≥3 domains. The research nurses offered help to participants who could not/had difficulty with filling out the questionnaire.

Health indicators

Chronic diseases

During the interviews the research nurses obtained self-reported data on the presence of common chronic diseases (self-reported diabetes, heart failure, malignancy, chronic obstructive pulmonary disease, incontinence, arthritis, osteoporosis, dizziness, lower urinary tract symptoms, depression, anxiety, dementia, vision, deafness, fracture, stroke/transient ischemic attack, and myocardial infarction)[17].

Disability

The Groningen Activities Restriction Scale (GARS) was used to measure disability to perform nine basic and nine instrumental activities of daily living (BADL and IADL, respectively)[18]. Sum scores for BADL and IADL were calculated separately; each sum score ranged from 9 (competent in all activities) to 36 (unable to perform any activity without help).

Cognitive function

Global cognitive function was assessed with the Mini-Mental State Examination (MMSE) with scores ranging from 0 (very severe cognitive impairment) to 30 points (optimal cognitive function)[19, 20].

Depressive symptoms

Depressive symptoms were assessed with the Geriatric Depression Scale-15 (GDS-15)[21]. The GDS-15 was only administered in participants with an MMSE score ≥19[22].

Loneliness

Feelings of loneliness were evaluated with the De Jong Gierveld Loneliness Scale, an 11-item questionnaire developed for use in older populations[23]; scores range from 0 (absence of loneliness) to 11 (severe loneliness). Administration of this loneliness scale was also restricted to participants with an MMSE score of ≥19.

Life satisfaction

Perceived life satisfaction was assessed by means of Cantril's ladder[24]; this is a visual analogue scale ranging from 1 (very unsatisfied) to 10 (very satisfied).

GP contact time

Data on GP contacts were derived from the electronic records of the participating GPs. The total number of contacts was defined as the sum of home visits and consultations in the year before the ISCOPE study was conducted. Since some electronic systems did

not allow data extraction, these data were available for 394 participants. To estimate the duration of GP contact time, a GP consultation was considered to last 10 minutes and a home visit (including traveling time) 30 minutes.

Statistical analyses

Scores on each of the three measures were dichotomized into two categories: identified as vulnerable/frail/complex or not identified.

Descriptive statistics were calculated for the total study population, and for the participants who were identified and who were not identified, separately. Since the continuous parameters were not normally distributed, differences between groups were compared with Mann-Whitney U tests. Chi-square tests were used to test differences in dichotomous data.

We compared the health indicators between older people who were identified by 1, 2 or 3 measures (8 combinations) with older persons who were not identified by all of the measures (the reference group) with Mann-Whitney U tests.

Data were analysed with SPSS 20.0 Windows; a p-value <0.05 was taken to be statistically significant.

RESULTS

Table 1 lists the sociodemographic and clinical characteristics. The participants had a median age of 83 (interquartile range [IQR] 79-87) years, 68.6% was female and 10.6% was living in a care home.

In our sample, the proportions of the participants identified according to the three measures were: 26.7% was identified as vulnerable according to the GP's intuition (n=219), 33.5% was frail according to Fried's frailty criteria (n=276), and 50.8% had complex problems according to the ISCOPE questionnaire (n=418) (Table 2).

Figure 1 shows the identified proportion according to the three measures. Of the total group, 10% (n=80) was vulnerable according to the GP, frail according to Fried's frailty phenotype, and had complex problems according to the ISCOPE questionnaire and 30% (n=247) was not identified by all three measures .

Vulnerability according to the GP, frailty according to Fried's frailty phenotype and complex problems according to the ISCOPE screening questionnaire were all related to the presence of more chronic diseases, higher GARS scores, lower MMSE scores, higher GDS-15 scores and lower scores on Cantril's ladder (all p<0.001) (Table 3). Complex problems according to the ISCOPE screening questionnaire and frailty according to the Fried frailty phenotype were also related to higher scores on the De Jong Gierveld Loneliness scale (p<0.001) (Table 3). The GP's intuition was not related to higher scores on this scale (Table 3).

Table 1. Characteristics of the study population.

	Total study population
	n=823
Age in years	83 (79-87)
Female	564 (68.5)
Care home	87 (10.6)
Low income	112 (13.6)
Low education	289 (35.1)
Number of diseases*	4 (3-6)
GARS	31 (24-40)
IADL	21 (15-28)
BADL	9 (9-12)
MMSE	28 (26-29)
GDS-15	1 (0-3)
De Jong Gierveld	2 (0-4)
Cantril's ladder	7 (7-8)
GP contact time during last year (min)	110 (50-250)

Data are presented as medians (IQR) or absolute numbers (%)

*self-reported diabetes, heart failure, malignancy, chronic obstructive pulmonary disease, incontinence, arthritis, osteoporosis, dizziness, lower urinary tract symptoms, depression, anxiety, dementia, vision, deafness, fracture, stroke/transient ischemic attack, myocardial infarction.

GARS=Groningen Activities Restriction Scale; IADL=Instrumental Activities of Daily Living; BADL= Basic Activities of Daily Living MMSE=Mini-Mental State Examination; GDS-15=Geriatric Depression Scale-15; GP=general practitioner

Table 2. Definition and prevalence of the three identification measures (including subdomains) in participants of the ISCOPE study aged 75 years and over.*

Identification measure	**Definition**	**Prevalence (n=823)**
GP's clinical intuition	Vulnerable for certain	219 (26.6)
Fried frailty criteria	≥ 3 Fried frailty criteria	276 (33.5)
	Unintentional weight loss	127 (15.4)
	Self-reported exhaustion	263 (32.0)
	Low energy consumption	211 (25.6)
	Slow gait speed	677 (82.3)
	Weak grip strength	376 (45.7)
ISCOPE screening questionnaire	≥ 3 domains with problems	418 (50.8)
	Functional domain	327 (39.7)
	Somatic domain	574 (69.7)
	Mental domain	569 (69.1)
	Social domain	441 (53.7)

Data are presented as absolute numbers (%)

*Older people with problems on 3 or 4 domains on the screening questionnaire were oversampled

GP=general practitioner

Table 3. Cross-sectional analyses of the identified older persons by one of the three measures (n=823)

	GP*			Fried's frailty phenotype*			ISCOPE screening questionnaire*		
	Vulnerable n=219	Not vulnerable n=559	p	Frail n=276	not Frail n=545	p	Complex problems n=418	No complex problems n=403	p
Age	83 (80-88)	82 (78-86)	0.001	84 (81-89)	81 (78-86)	<0.001	83 (80-87)	81 (78-85)	<0.001
Female	150 (68.5)	383 (68.5)	0.983	189 (68.5)	373 (68.4)	0.847	301 (72.0)	261 (64.8)	0.033
Institutionalized	32 (14.6)	46 (8.2)	0.008	59 (21.4)	27 (5.0)	<0.001	60 (14.4)	26 (6.5)	<0.001
Number of diseases#	5 (3-6)	4 (2-5)	<0.001	5 (3-6)	4 (2-5)	<0.001	5 (3-6)	3 (2-5)	<0.001
GARS	37 (29-49)	29 (23-37)	<0.001	41 (31-52)	27 (22-34)	<0.001	36 (28-45)	27 (21-33)	<0.001
IADL	27 (19-33)	19 (14-26)	<0.001	29 (21-34)	18 (13-24)	<0.001	25(19-32)	18 (12-24)	<0.001
BADL	11 (9-17)	9 (9-11)	<0.001	12 (9-18)	9 (9-10)	<0.001	10 (9-14)	9 (9-10)	<0.001
MMSE	27 (24-29)	28 (26-28)	<0.001	27 (25-29)	28 (26-29)	<0.001	28 (26-29)	28 (27-29)	<0.001
GDS-15	2 (1-4)	1 (0-3)	<0.001	3 (1-5)	1 (0-2)	<0.001	3 (1-4)	1 (0-2)	<0.001
De Jong Gierveld	3 (0-5)	2 (1-4)	0.228	3 (1-5)	2 (0-4)	0.006	3 (1-6)	1 (0-3)	<0.001
Cantril's ladder	7 (6-8)	7 (7-8)	0.001	7 (6-8)	7 (7-8)	<0.001	7 (6-8)	8 (7-8)	<0.001
GP contact time during last year (min)	220 (100-360)	90 (40-170)	<0.001	180 (90-390)	100 (40-180)	<0.001	160 (75-310)	90 (40-170)	<0.001

Data are medians (IQR) or number (%); p-values were obtained by chi-square tests (categorical data) or Mann Witney U tests (continuous data)

* 44 participants had missing values for the GP's intuition; 2 participants had missing values for Fried's frailty phenotype; 1 participant had missing values for the ISCOPE screening questionnaire, 1 participant had missing values for the GP's intuition and the ISCOPE screening questionnaire

including self-reported diabetes, heart failure, malignancy, COPD, incontinence, arthritis, osteoporosis, dizziness, LUTS, depression, anxiety, dementia, vision, deafness, fracture, stroke/TIA, myocardial infarction.

Abbreviations: GP=general practitioner; GARS=Groningen Activities Restriction Scale; IADL=Instrumental Activities of Daily living; BADL= Basic Activities of daily living MMSE=Mini-Mental State Examination; GDS-15=Geriatric Depression Scale-15

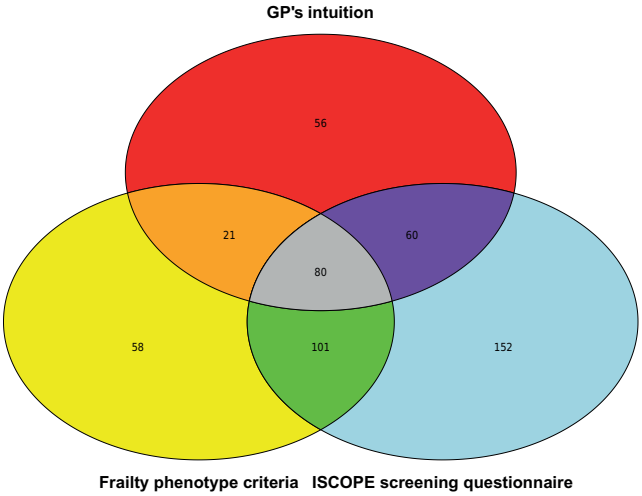


Figure 1. Venn diagram depicting proportion (number of participants) identified by the three measures (GP's intuition, Fried frailty phenotype criteria, and the ISCOPE screening questionnaire). Of the total study population, 48 participants had missing values on one of the measures and 247 participants had no problems according to all three; these latter groups of older persons are not included in the diagram.

Table 4 shows the median scores on various health indicators for each of the 8 combinations of the measures. Older people classified as vulnerable according to the GP's clinical intuition had more contact time with the GP compared with the reference group (not identified by all three measures, n=247). For the other health indicators, no significant differences were found between older persons identified by the GP's clinical intuition and the reference group.

Compared with the reference group, older people with frailty according to Fried's frailty criteria had a higher GARS score, higher GDS score and had more contact time with their GP, but no higher scores on the MMSE and the De Jong Gierveld Loneliness scale compared to the reference group (Table 4).

People with complex problems according to the ISCOPE screening questionnaire had higher scores on the GARS, GDS-15, the De Jong Gierveld Loneliness Scale and more GP-contact time compared with the reference group (Table 4).

In general, the Fried frailty phenotype was most strongly associated with disability and the ISCOPE screening questionnaire most strongly with loneliness. Compared with the reference group, participants who were identified by two or three of the three measures generally had more chronic diseases, higher scores on the GARS, lower scores on the MMSE, higher scores on the GDS-15 and more GP contact time.

Table 4. Cross-sectional comparison of older persons with and without complex health problems according to the three identification measures (n=823)

	Identification measure													
GP's clinical intuition	no	yes		no		no		yes		yes		no		yes	
Fried frailty phenotype criteria	no	no		yes		no		yes		no		yes		yes	
ISCOPE screening questionnaire	no	no		no		yes		no		yes		yes		yes	
	n=247 reference group	n=56*	p**	n=58*	p**	n=152*	p**	n=21*	p**	n=60*	p**	n=101*	p**	n=80*	p**
Number of diseases	2 (3-4)	2 (3-5)	0.369	4 (2-5)	0.031	4 (3-6)	<0.001	4 (2-5)	0.491	5 (3-7)	<0.001	5 (3-7)	<0.001	6 (5-7)	<0.001
GARS (points)	24 (21-30)	27 (22-34)	0.117	36 (28-42)	<0.001	29 (24-36)	<0.001	39 (29-51)	<0.001	36 (29-41)	<0.001	39 (30-51)	<0.001	49 (38-57)	<0.001
MMSE (points)	28 (27-29)	28 (26-29)	0.150	28 (26-29)	0.091	28 (27-29)	0.703	27 (23-29)	0.014	26 (25-28)	<0.001	28 (26-29)	0.001	27 (23-29)	<0.001
GDS-15 (points)	1 (0-1)	1 (0-1)	0.620	2 (1-3)	<0.001	2 (1-3)	<0.001	2 (1-3)	0.008	3 (1-4)	<0.001	3 (2-5)	<0.001	3 (2-5)	<0.001
De Jong Gierveld (points)	1 (0-3)	1 (0-3)	0.352	2 (0-3)	0.582	3 (1-5)	<0.001	2 (0-3)	0.842	4 (1-6)	<0.001	4 (1-7)	<0.001	3 (1-6)	<0.001
GP contact time during last year (min)	70 (30-110)	160 (92-277)	<0.001	110 (70-300)	0.007	130 (60-220)	<0.001	165 (50-320)	0.069	190 (95-310)	<0.001	115 (42-280)	0.015	330 (178-588)	<0.001

* 44 participants had missing values for the GP's intuition; 2 participants had missing values for Fried's frailty phenotype; 1 participant had missing values for the ISCOPE screening questionnaire, 1 participant had missing values for the GP's intuition and the ISCOPE screening questionnaire these participants were not included.

** Mann-Whitney U test compared to no complex health problems according to all concepts (reference group, first column)

Data are presented as medians (IQR)

GP=general practitioner; ISCOPE=Integrated Systematic Care for Older People; GARS=Groningen Activities Restriction Scale; MMSE=Mini-mental state examination; GDS=Geriatric Depression Scale

DISCUSSION

In this study, three measures (i.e. the GP's clinical intuition, the Fried frailty criteria and the ISCOPE screening questionnaire) were selected for a comparison to identify problems in multiple health domains in a primary care population of older people. These three measures differed substantially with regard to the number of older people identified; however, irrespective of the measure used, identified older people had more disability, poorer cognition, more depressive symptoms, more feelings of loneliness and poorer life satisfaction.

Comparison with other studies

The first measure, the GP's intuition, was selected because most GPs have a clear image of vulnerable older people in mind based on 'gut feeling'[25]. The question was if this intuition on vulnerability is an identification measure to identify older persons with problems in multiple health domains. With the GPs intuition, older people with multiple functional, somatic and mental problems were identified. However, no differences were found for the De Jong Gierveld Loneliness Scale between participants classified as vulnerable according to the GP's intuition and participants who were not vulnerable. This suggests that the GPs intuition might not be an identification measure for loneliness. This is in line with another study concluding that GPs rarely ask about loneliness[26].

The second measure, the Fried frailty phenotype[5], was selected because it is an internationally recognised and validated measure for frailty. The results of the present study imply that the Fried frailty phenotype could also be considered as a measure to identify older people with problems in multiple health domains in primary care, because it is associated with disability, depressive symptoms and more GP contact time. However, the Fried frailty criteria did not show a strong association with loneliness.

The ISCOPE screening questionnaire covers four health domains that measure functional, somatic, mental and social problems[12]. In this study, the ISCOPE screening questionnaire was associated with both disability and depressive symptoms, and was the only measure that had a strong association with loneliness. Therefore, the ISCOPE screening questionnaire can be considered as an identification measure for problems in multiple health domains in primary care.

In the present study, the proportion of participants identified ranged from about 25% (GP's intuition) to about 50% of the study population (ISCOPE screening questionnaire). The prevalence of the frailty phenotype was substantially higher than in other studies investigating this measure conducted in both primary care[10, 27] and in research settings[5]. These differences can be explained by our relatively older population.

Strengths and weaknesses

The present study has several strengths. First, being population-based with few exclusion criteria this increases the external validity of our results. Second, the health indicators that were used as outcomes in this study were measured with validated questionnaires by research nurses during home visits, thereby increasing the reliability and completeness of the measurements.

A major limitation of this study is its cross-sectional design. Therefore, we could not compare the predictive value of the three measures on future relevant health indicators, such as incident disease and mortality.

Implications for primary care

The three measures included in this study are all appropriate for identification of older people with problems in multiple health domains in primary care. None of these measures can be recommended as the most appropriate measure, because the population identified differs for each of the three measures. The choice of a measure should depend on the intended intervention of the GP. For example, if a GP is planning an intervention for disability, the Fried frailty criteria might be the most appropriate measure. In contrast, if the intervention aims at loneliness, then the ISCOPE screening questionnaire might be the best choice. However, before these interventions can be conducted, the cost-effectiveness of such interventions remains to be proven.

Moreover, when selecting a measure, GPs should also consider the relative workload involved with each measure. For example, the administration of the Fried frailty measure is difficult because of the performance tests involved. In contrast, the ISCOPE screening questionnaire can be sent by post, and is easy to administer. The GP's intuition about vulnerability does not require additional workload as it is readily available.

Conclusion

This study compared three measures to identify problems in multiple health domains in older people in primary care. Older people identified by any of the three measures are at increased risk for poor health. Therefore, each instrument might be appropriate for identification of older people with problems in multiple health domains for proactive interventions to prevent poor health outcomes, although the cost-effectiveness of such interventions remains to be proven. A decision about an appropriate measure should take into account the aims of the GP in relation to the identification of older patients with problems in multiple health domains.

REFERENCES

1. Drewes YM, Koenen JM, de Ruijter W et al. GPs' perspectives on preventive care for older people: a focus group study. Br J Gen Pract 2012;62(604):765-772.
2. Alessi CA, Josephson KR, Harker JO, Pietruszka FM, Hoyl MT, Rubenstein LZ. The yield, reliability, and validity of a postal survey for screening community-dwelling older people. J Am Geriatr Soc 2003;51(2):194-202.
3. Beales DL, Tulloch AJ. Community care of vulnerable older people: cause for concern. Br J Gen Pract 2013;63(615):549-550.
4. Fletcher AE, Jones DA, Bulpitt CJ, Tulloch AJ. The MRC trial of assessment and management of older people in the community: objectives, design and interventions [ISRCTN23494848]. BMC Health Serv Res 2002;2(1):21.
5. Fried LP, Tangen CM, Walston J et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56(3):M146-M156.
6. Gobbens RJ, van Assen MA, Luijkx KG, Wijnen-Sponselee MT, Schols JM. The Tilburg Frailty Indicator: psychometric properties. J Am Med Dir Assoc 2010;11(5):344-355.
7. Peters LL, Boter H, Buskens E, Slaets JP. Measurement Properties of the Groningen Frailty Indicator in Home-Dwelling and Institutionalized Elderly People. J Am Med Dir Assoc 2012;13(6):546-551.
8. Saliba D, Elliott M, Rubenstein LZ et al. The Vulnerable Elders Survey: a tool for identifying vulnerable older people in the community. J Am Geriatr Soc 2001;49(12):1691-1699.
9. Rockwood K, Song X, MacKnight C et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173(5):489-495.
10. Hoogendijk EO, van der Horst HE, Deeg DJ et al. The identification of frail older adults in primary care: comparing the accuracy of five simple instruments. Age Ageing 2013;42(2):262-265.
11. Grant RW, Ashburner JM, Hong CC, Chang Y, Barry MJ, Atlas SJ. Defining Patient Complexity From the Primary Care Physician's Perspective A Cohort Study. Ann of Intern Med 2011;155(12):797-804.
12. Poot AJ, den Elzen WP, Blom JW, Gussekloo J. Level of satisfaction of older persons with their general practitioner and practice: role of complexity of health problems. PLoS One 2014;9(4):e94326.
13. Chan OY, van Houwelingen AH, Gussekloo J, Blom JW, den Elzen WP. Comparison of quadriceps strength and handgrip strength in their association with health outcomes in older adults in primary care. Age (Dordr) 2014;36(5):9714.
14. Drewes YM, Blom JW, Assendelft WJ, Stijnen T, den Elzen WP, Gussekloo J. Variability in vulnerability assessment of older people by individual general practitioners: a cross-sectional study. PLoS One 2014;9(11):e108666.
15. van Iersel MB, Jansen DR, Rikkert MG. [Frailty in the elderly]. Ned Tijdschr Geneeskd 2009;153:A183.
16. Orme JG, Reis J, Herz EJ. Factorial and discriminant validity of the Center for Epidemiological Studies Depression (CES-D) scale. J Clin Psychol 1986;42(1):28-33.
17. Lutomski JE, Baars MA, Schalk BW et al. The development of the Older Persons and Informal Caregivers Survey Minimum DataSet (TOPICS-MDS): a large-scale data sharing initiative. PLoS One 2013;8(12):e81673.
18. Bootsma-van der Wiel A, Gussekloo J, De Craen AJ et al. Disability in the oldest old: "can do" or "do do"? J Am Geriatr Soc 2001;49(7):909-914.
19. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12(3):189-198.

20. Heeren TJ, Lagaay AM, von Beek WC, Rooymans HG, Hijmans W. Reference values for the Mini-Mental State Examination (MMSE) in octo- and nonagenarians. J Am Geriatr Soc 1990;38(10):1093-1096.
21. Weeks SK, McGann PE, Michaels TK, Penninx BW. Comparing various short-form Geriatric Depression Scales leads to the GDS-5/15. J Nurs Scholarsh 2003;35(2):133-137.
22. Gussekloo J, Westendorp RG, Remarque EJ, Lagaay AM, Heeren TJ, Knook DL. Impact of mild cognitive impairment on survival in very elderly people: cohort study. BMJ 1997;315(7115):1053-1054.
23. de Jong-Gierveld J, Kamphuls F. The Development of a Rasch-Type Loneliness Scale. Appl Psychl Meas 1985;9(3):289-299.
24. Cantril H. The pattern of human concern. Rutgers University Press; 1965.
25. Stolper E, Van de Wiel M, Van Royen P, Van der Weijden T, Dinant GJ. Gut feelings as a third track in general practitioners' diagnostic reasoning. J Gen Intern Med 2011;26(2):197-203.
26. van Ravesteijn H., Lucassen P, van der Akker M. GPs' experiences with loneliness. Aust Fam Physician 2008;37(11):973-976.
27. Drey M, Wehr H, Wehr G et al. The frailty syndrome in general practitioner care: a pilot study. Z Gerontol Geriatr 2011;44(1):48-54.



7

COMPARISON OF QUADRICEPS STRENGTH AND HANDGRIP STRENGTH IN THEIR ASSOCIATION WITH HEALTH OUTCOMES IN OLDER ADULTS IN PRIMARY CARE

On Ying A. Chan, Anne H. van Houwelingen, Jacobijn Gussekloo,
Jeanet W. Blom and Wendy P.J. den Elzen

Age (Dordr). 2014 Oct;36(5):9714. doi: 10.1007/s11357-014-9714-4. Epub 2014 Oct 4.

ABSTRACT

Sarcopenia is thought to play a major role in the functional impairment that occurs with old age. In clinical practice, sarcopenia is often determined by measuring handgrip strength. Here, we compared the lower limb quadriceps strength to the handgrip strength in their association with health outcomes in older adults in primary care. Our study population consisted of older adults (n=764, 68.2% women, median age 83) that participated in the Integrated Systemic Care for Older People (ISCOPE) study. Participants were visited at baseline to measure quadriceps strength and handgrip strength. Data on health outcomes were obtained at baseline and after 12 months (including life satisfaction, disability in daily living, GP contact-time and hospitalization). Quadriceps strength and handgrip strength showed a weak association (β=0.42 [95% CI 0.33-0.50]; R^2= 0.17). Quadriceps strength and handgrip strength were independently associated with health outcomes at baseline, including quality of life, disability in daily living, GP contact-time, hospitalization and gait speed. Combined weakness of the quadriceps and handgrip distinguished a most vulnerable subpopulation that presented with the poorest health outcomes. At follow-up, handgrip strength showed an association with quality of life (β=0.05; P=0.002) and disability in daily living (β=-0.5; P=0.004). Quadriceps weakness did not further contribute to the prediction of the measured health outcomes. We conclude that quadriceps strength is only moderately associated with handgrip strength in an older population and that the combination of quadriceps strength and handgrip strength measurements may aid in the identification of older adults in primary care with the poorest health outcomes. In the prediction of poor health outcomes, quadriceps strength measurements do not show an added value to the handgrip strength.

INTRODUCTION

Sarcopenia, defined as the degenerative loss of skeletal muscle tissue associated with aging, is thought to play a major role in the functional impairment that occurs with old age[1, 2]. In clinical practice, handgrip strength is often used as a surrogate measure representative of the sarcopenic condition, as measuring handgrip strength is a simple, accessible and inexpensive method to use[3]. Handgrip strength has been shown to associate with several adverse health outcomes in the elderly, including functional impairment[4-7], morbidity[8], hospitalization[9] and mortality[10-12].

Although upper limb muscle measurements correlate with several health outcomes, lower limb muscle measurements may be a better parameter for mobility outcomes. In clinical practice, lower limb muscle strength measurements often consist of quadriceps strength measurements during knee extension and flexion[3]. A previous study investigating the relationship between handgrip strength and lower limb muscle strength reported a strong association with correlation coefficients varying from 0.70 to 0.72[3, 13]. Similar to handgrip strength, quadriceps strength correlates with various negative health outcomes in older adults. These include functional impairment[6, 7, 14, 15], hospitalization[9] and mortality[10, 11].

Several studies have investigated the correlation of handgrip strength and quadriceps strength on disability items related to mobility[6, 7]. However, these studies all analyzed the correlation separately for the handgrip strength and quadriceps strength, and did not investigate the correlation of these parameters in relation to each other to determine whether the two muscle strength parameters have complementary value. In this study, we investigated both lower limb quadriceps strength and handgrip strength in their association with health outcomes in older adults in primary care.

METHODS

Study population

The study population consisted of older adults aged 75 and over who participated in the Integrated Systematic Care for Older People (ISCOPE) study. The ISCOPE study is a pragmatic cluster-randomized controlled trial that compared a proactive approach by the general practitioner (GP) with the usual care provided by the GP in monitoring the health status of older adults with complex problems. The presence of complex problems was defined as having problems in at least 3 of the 4 predefined domains: functional, somatic, psychological and social, and was assessed by the ISCOPE screening questionnaire[16].

The ISCOPE study population was recruited from 59 participating primary care practices and all registered adults aged 75 and above were targeted (n=12,066). Persons who were deceased, too ill, non-Dutch speaking, admitted to a nursing home, or judged unsuitable according to their GP were excluded (n=590). Of the remaining 11,476 individuals, whom were sent a written screening questionnaire, 7285 were completed and returned.

A random sample of the 7285 participants was visited at home to obtain data on socio-demographic characteristics and to partake in additional questionnaires. Based on the outcomes of the screening questionnaire, individuals with problems in 3 or more domains were all visited and interviewed. Of the participants with problems in 2 domains, 60% was interviewed. Of the individuals with no problems or problems in 1 domain, 15% was interviewed. In total, 2713 participants were visited at home to obtain data on socio-demographic characteristics, residency, functional status and the presence of disease. After one year, participants were revisited to partake in the same questionnaires to obtain follow-up information.

In the ISCOPE study, older adults with complex problems were provided the usual care by the GP or provided a proactive approach by the GP, which consisted of a care plan that was drafted together with the participant and informal caregiver. The priorities and goals of the older adult and informal caregiver were taken as a starting point. Actions to be taken and evaluation plans for follow-up were formulated by the GP together with the participant.

For the purpose of the present analyses, a subgroup of 823 participants was randomly selected from 22 of the 59 participating general practices (both control and intervention practices). Participants with complex problems were oversampled. The 823 participants received an additional questionnaire during the home visit at baseline, and additional measurements on handgrip strength, quadriceps strength and gait speed were obtained by the research nurses. All participants gave written informed consent; for participants with severe cognitive impairment, informed consent was obtained from a proxy. The study was approved by the Medical Ethics Committee of Leiden University Medical Centre. For the present analysis, 764 participants were included with valid quadriceps and handgrip strength measurements. Follow-up data was available for 570 participants.

Study parameters

Determinants

Muscle strength

Muscle strength measurements for the handgrip and the lower limb were obtained during the home visits at baseline.

Handgrip strength was measured using a Jamar hand dynamometer (Sammons Preston Inc. Bolingbrook, IL). Participants were asked whether they were left or right handed to determine their dominant side. To measure handgrip strength, the participant was instructed to stand up and hold the dynamometer in the dominant hand with the arm parallel to the body without squeezing the arm against the body. The width of the handle was adjusted to the size of the participant's hand to ensure that the middle phalanx rested on the inner handle. The participant was allowed to perform one test trial. After this, three measurements followed and the best score was used for analysis[17-19]. Handgrip strength was expressed in kilograms; cut-off points to determine weak (versus normal) handgrip strength were derived from Fried et al.[20] (for male participants <30 kg and for female participants <18 kg). Subjects unable to complete the handgrip strength test due to physical limitations were considered to have weak handgrip strength.

Lower limb muscle strength was measured for the quadriceps using the Microfet2®, a hand held dynamometer (Hoggan Health Industries Inc. Salt Lake City, UT). A hand held dynamometer is a widely used, reliable, and valid instrument to measure isometric peak force, also in the elderly patient[21, 22]. The Microfet2® has a high (inter-rater) reliability and validity in measuring quadriceps strength[23-25]. To measure knee extension, the participant was seated in a straight-back chair without armrests. The participants stabilized their position by holding on to the seat of the chair and knees were positioned at a resting angle of 90°. The dynamometer was placed just above the ankles against the shins. Participants were asked to push against the dynamometer to measure isometric strength. The participant was allowed to perform one test trial. After this, three measurements followed and the best score was used for analysis. The peak force was measured in kilograms. The median (adjusted for sex) was used as a cut-off point to determine weak (versus normal) quadriceps strength. Among the 764 subjects included in the analysis, 66 subjects were hindered by physical limitations during the quadriceps strength assessment (8.6%). Subjects unable to complete the knee extension test due to physical limitations were considered to have weak quadriceps strength. Quadriceps strength was measured in both legs; measurements of the dominant and non-dominant side were highly correlated (R^2= 0.75, β= 0.87; Table 2) indicating consistent quadriceps measurements. Participants were asked whether they were left or right handed to determine their dominant side. For further analyses the quadriceps strength of the dominant leg was used.

Health outcomes

Quality of life

Quality of life was assessed at baseline and follow-up using the EQ5D+c questionnaire, a generic instrument developed by the EuroQol Group to value health (extended with a cognitive dimension)[26, 27]. Quality of life was additionally scored using the Visual Analogue Scale for perceived health status, ranging from 0 (worst imaginable health status) to 100 (best imaginable health status) and the Cantril ladder of life, a visual analogue scale on the perceived quality of life, ranging from 1 (very unsatisfied) to 10 (very satisfied)[28].

Functional status

Disability in basic (BADL) and instrumental activities of daily living (IADL) was measured at baseline and follow-up with the Groningen Activities Restriction Scale (GARS)[29]. The GARS is a questionnaire that assesses disability in the competence of nine BADL items and nine IADL items[30]. A sum score was calculated for BADL and IADL separately; each sum score ranged from 9 (competent in all activities) to 36 (unable to perform any activity without help).

GP contact-time

The number of GP contacts, including home-visits and consultations, were extracted from the electronic patient records (EPR). GP contact-time at baseline was calculated from the GP contacts during the year before ISCOPE and GP contact-time at follow-up was calculated from the GP contacts in the year during follow-up. Consultations were estimated at 10 minutes of GP contact and home visits at 30 minutes. EPR data were available for 359 participants.

Hospitalization

Participants were asked whether they had been admitted in the hospital in the past 12 months.

Gait speed

Gait speed was assessed at baseline with a 12 m walking test[31, 32]. A 3 m course was denoted by tape measurement, along which the participants were instructed to walk up and down. Participants were requested to walk as quickly as possible from a standing start position and total time was measured using a stopwatch. Use of a walking aid was allowed. Gait speed was calculated using distance in meters and time in seconds (meters per second [m/s]).

Other parameters

Socio-demographic characteristics

Participants were interviewed to obtain information on their sex, age, living situation (independent and alone, independent with others, residential care home or residential nursing home), income (state pension only or state pension with additional income) and educational level (primary school, high school, vocational school or university).

Chronic diseases

Data on common chronic diseases were self-reported and obtained during the interview at baseline. Chronic diseases included self-reported diabetes, heart failure, cancer, chronic obstructive pulmonary disease (COPD), incontinence, arthritis, osteoporosis, dizziness, lower urinary tract symptoms (LUTS), depression, anxiety, dementia, vision, deafness, fracture, stroke/transient ischemic attack (TIA), and myocardial infarction. The number of chronic diseases was used as a measure of multi-morbidity.

Body weight

The body weight of the participants was measured in kilograms (kg) during the home visits.

Statistical analyses

Medians and interquartile ranges (IQR) were used to describe continuous variables and proportions were used for categorical variables. Handgrip and quadriceps strengths were normalized using square root transformation followed by standardization into Z-scores.

First, we analyzed the correlation between quadriceps strength and handgrip strength using linear regression. The cross-sectional association with health outcomes was analyzed both separately and combined for the handgrip and quadriceps strength using linear or logistic regression models adjusting for age and sex. In addition, we performed a longitudinal analysis investigating the predictive value of the handgrip and quadriceps strength on health outcomes after one year of follow-up, separately and combined. This analysis was additionally adjusted for the baseline values of the health outcomes measured.

Second, we compared characteristics and health outcomes for different handgrip and quadriceps strength categories, both cross-sectionally and prospectively. Groups were defined by having either normal handgrip and normal quadriceps strength, weak handgrip and normal quadriceps strength, weak quadriceps and normal handgrip strength, or weak handgrip and weak quadriceps strength. The four groups were compared using general linear model (GLM) univariate analyses. Health outcomes at baseline were corrected for age and sex, and health outcomes at follow-up were corrected for age, sex

and baseline values of the health outcome. A P-value of <0.05 was considered statistically significant. Data were analyzed using SPSS 20.0 for Windows.

RESULTS

Study population

The baseline characteristics of our population are described in Table 1. The median age of the participants was 83 (interquartile range [IQR] 79-87). Among the participants, 68.2%

Table 1. Baseline characteristics of the study population.

	Total (n=764)	Men (n=243; 31.8%)	Women (n=521; 68.2%)
Age (yr)	83 [79; 87]	82 [78; 87]	83 [79; 87]
Living situation			
Living alone	434 (57.2)	86 (36.1)	348 (66.8)
Residence in a long term facility	74 (9.7)	13 (5.5)	61 (11.7)
Low income[1]	101 (13.3)	23 (9.6)	78 (15.0)
Low education[2]	266 (35.0)	61 (25.6)	205 (39.3)
Number of chronic diseases[3]	4 [2; 6]	3 [2; 5]	4 [3; 6]
Weight (kg)	72 [63; 82]	80 [71; 87]	69 [60; 77]
Quality of life			
Cantril's ladder	7 [7; 8]	7 [7; 8]	7 [7; 8]
EQ5D+c	0.81 [0.65; 0.84]	0.81 [0.68; 0.89]	0.78 [0.65; 0.84]
Visual Analogue Scale	70 [60; 75]	70 [60; 75]	70 [60; 75]
Functioning			
GARS	30 [24; 38]	29 [24; 39]	30 [24; 38]
BADL	9 [9; 11]	9 [9; 11]	9 [9; 12]
IADL	21 [15; 27]	20 [15; 27]	21 [15; 27]
GP contact-time (minutes) [4]	110 [50; 220]	80 [40; 160]	120 [60; 260]
Gait speed (m/s)	0.52 [0.31; 0.71]	0.59 [0.40; 0.77]	0.48 [0.30; 0.66]
Handgrip strength (kg)[5]	20 [16; 28]	30 [25; 36]	18 [14; 22]
Quadriceps strength (kg)[5]	25 [17; 36]	32 [20; 41]	23 [16; 33]

Data are numbers (%) or median [IQR].

1 State pension only.

2 Primary school only.

3 Including self-reported diabetes, heart failure, cancer, chronic obstructive pulmonary disease, incontinence, arthritis, osteoporosis, dizziness, lower urinary tract symptoms, depression, anxiety, dementia, impaired vision, deafness, fracture, stroke/transient ischemic attack, myocardial infarction.

4 GP contact information was available for 359 participants.

5 Median handgrip and quadriceps strength differed between men and women (Mann-Whitney *U*, *P* <0.001).

were female, 57.2% were living alone and 9.7% were living in a care home. The median number of chronic diseases was 4 (IQR 2-6). Perceived life satisfaction as measured by Cantril's ladder was 7 (IQR 7-8) and quality of life measured by the EQ5D+c index was 0.81 (IQR 0.65-0.84). The median scores of disability in the basic (BADL) and instrumental activities of daily living (IADL) were 9 (IQR 9-11) and 21 (IQR 15-27) respectively. Of the participants, 30.9% was considered frail according to the definition by Fried et al.[20].

The median handgrip strength was 30 kg (IQR 25-36) for male participants and 18 kg (IQR 14-22) for female participants (P <0.001). The median quadriceps strength was 32 kg (IQR 20-41) for men and 23 kg (IQR 16-33) for women (P <0.001).

Correlation handgrip strength and quadriceps strength

In this study population, the correlation between handgrip strength and quadriceps strength was weak; the effect estimate (β) of the handgrip strength on the quadriceps strength was 0.42 (95% confidence interval [CI] 0.33-0.50) and the coefficient of determination (R^2) was 0.17 (adjusted for age and sex; Table 2). When outliers were excluded from the analysis the correlation between handgrip and quadriceps strength was even poorer (β= 0.32 [95% CI 0.22-0.42], R^2= 0.13). Figure 1 depicts the correlation between handgrip and quadriceps strength, separately for men and women. The effect estimate and coefficient of determination for men (adjusted for age) were 0.34 (95% CI 0.18-0.51) and 0.12, and for women 0.44 (95% CI 0.34-0.55) and 0.14.

Table 2. Association between the quadriceps strength and the handgrip strength.

Per unit[1] change in	Outcome	Crude			Adjusted for age & sex		
		R^2	β (95% CI)	*P*-value	R^2	β (95% CI)	*P*-value
Handgrip strength	Quadriceps strength (dominant side)	0.16	0.44 (0.37; 0.52)	<0.001	0.17	0.42 (0.33; 0.50)	<0.001
Quadriceps strength (dominant side)	Quadriceps strength (non-dominant side)	0.75	0.87 (0.83; 0.91)	<0.001	0.75	0.87 (0.83; 0.90)	<0.001

1 Handgrip and quadriceps strength measurements were normalized by square root transformation and standardized into Z-scores.

Association between the handgrip or quadriceps strength and health outcomes at baseline

Table 3 shows the cross-sectional analysis of the association between the handgrip strength and several health outcomes, unadjusted (Model I) and adjusted (Model II) for quadriceps strength. In the univariate analyses, handgrip strength was significantly associated with quality of life measured by EQ5D+c (β= 0.08 [95% CI 0.06; 0.10]), disability in daily living as scored using GARS (β= -5.2 [95% CI -6.2; -4.3]), GP contact-time (β= -34 minutes [95% CI -63; -5]), hospitalization (Odds Ratio (OR)= 0.6 [95% CI 0.5; 0.8]) and gait speed (β= 0.12 m/s [95% CI 0.10; 0.15]). When quadriceps strength was included in

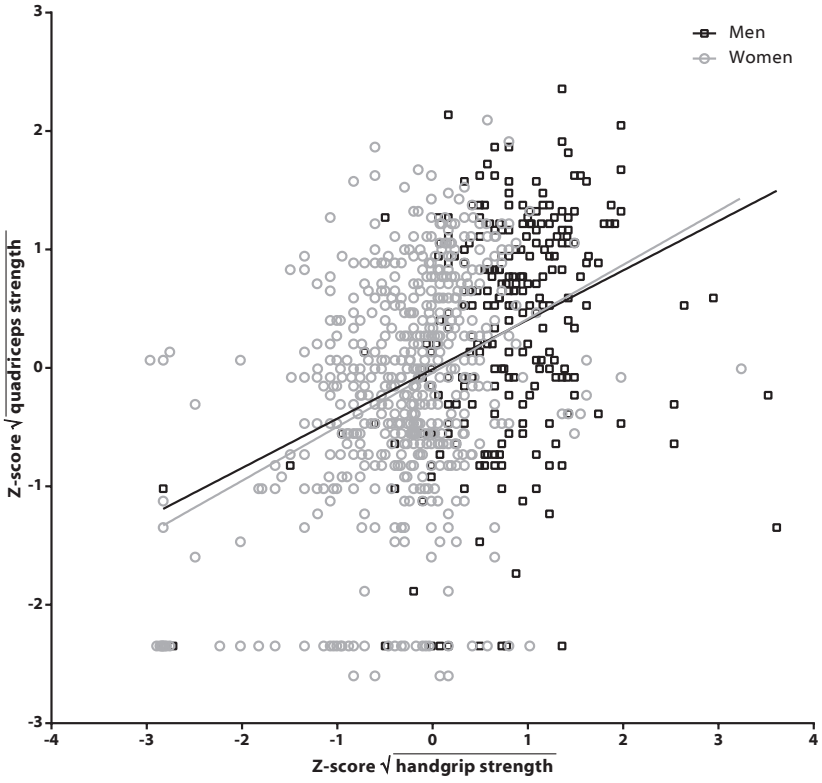


Figure 1. Scatter plot showing the relationship between the handgrip strength and the quadriceps strength. Regression lines are marked separately for men and women. Handgrip and quadriceps strength measurements were normalized using square root transformation followed by standardization into Z-scores. Correlation estimates for men (adjusted for age): R^2=0.12, β=0.34 (95% CI 0.18-0.51); women (adjusted for age): R^2=0.14, β=0.44 (95% CI 0.34-0.55).

the multivariate model, the predictive value improved as demonstrated by elevated R^2 scores and significant F-ratios and model χ^2. Handgrip strength remained significantly associated with most health outcomes except for GP contact-time (P =0.082). Quadriceps strength was also significantly associated with poorer scores on the measured health outcomes, independently of the handgrip strength: EQ5D+c (β= 0.09 [95% CI 0.07; 0.11]), GARS (β= -3.4 [95% CI -4.1; -2.7]), GP contact-time (β= -28 minutes [95% CI -52; -4]), hospitalization (OR=0.8 [95% CI 0.7; 1.0]) and gait speed (β= 0.10 m/s [95% CI 0.08; 0.12]). The effect estimates of the quadriceps strength were comparable to those for the handgrip strength except for EQ5D+c: β for quadriceps strength was 0.09 (95% CI 0.07; 0.11) and 0.04 (95% CI 0.02; 0.07) for handgrip strength.

Table 3. Analysis of the handgrip and quadriceps strength on health outcomes at baseline.

	Model I[1] (handgrip strength)					Model II[1] (combination of handgrip and quadriceps strength)						
	Model statistics			per unit handgrip strength		Model statistics			per unit handgrip strength		per unit quadriceps strength	
	$R^{2,2}$	*F-ratio*/χ^2	*P*-value	β/OR (95% CI)	*P*-value	$R^{2,2}$	*F-ratio*/χ^2	*P*-value	β/OR (95% CI)	*P*-value	β/OR (95% CI)	*P*-value
EQ5D+c	0.07	18.01	<0.001	0.08 (0.06; 0.10)	<0.001	0.17	91.03	<0.001	0.04 (0.02; 0.07)	0.001	0.09 (0.07; 0.11)	<0.001
GARS	0.28	98.41	<0.001	-5.2 (-6.2; -4.3)	<0.001	0.36	85.39	<0.001	-3.8 (-4.8; -2.9)	<0.001	-3.4 (-4.1; -2.7)	<0.001
- BADL	0.14	39.60	<0.001	-1.6 (-2.0; -1.2)	<0.001	0.20	61.93	<0.001	-1.1 (-1.5; -0.7)	<0.001	-1.2 (-1.6; -0.9)	<0.001
- IADL	0.31	111.86	<0.001	-3.6 (-4.3; -3.0)	<0.001	0.37	70.90	<0.001	-2.8 (-3.4; -2.1)	<0.001	-2.1 (-2.6; -1.6)	<0.001
GP contact-time (minutes)[3]	0.14	18.70	<0.001	-34 (-63; -5)	0.024	0.15	5.30	0.022	-27 (-56; 3)	0.082	-28 (-52; -4)	0.022
Hospitalization	0.05	26.30	<0.001	0.6 (0.5; 0.8)	<0.001	0.06	4.77	0.029	0.7 (0.5;0.9)	0.002	0.8 (0.7; 1.0)	0.028
Gait speed (m/s)	0.26	88.92	<0.001	0.12 (0.10; 0.15)	<0.001	0.37	121.55	<0.001	0.08 (0.06; 0.11)	<0.001	0.10 (0.08; 0.12)	<0.001

1 Both models are adjusted for sex and age.

2 For the outcome 'Hospitalization' the Nagelkerke R^2 was used to estimate R^2.

3 GP contact information was available for 359 participants.

Table 4. Prospective analysis of baseline handgrip and quadriceps strength on health outcomes after one year of follow-up.

	Model I[1] (handgrip strength)					Model II[1] (combination of handgrip and quadriceps strength)						
	Model statistics			per unit handgrip strength		Model statistics			per unit handgrip strength		per unit quadriceps strength	
	$R^{2,2}$	*F-ratio*/ χ^2	*P*-value	β/OR (95% CI)	*P*-value	$R^{2,2}$	*F-ratio*/ χ^2	*P*-value	β/OR (95% CI)	*P*-value	β (95% CI)	*P*-value
EQ5D+c	0.29	58.54	<0.001	0.05 (0.02; 0.08)	<0.001	0.30	2.09	0.149	0.05 (0.02; 0.08)	0.002	0.02 (-0.01; 0.04)	0.149
GARS	0.77	460.27	<0.001	-0.4 (-1.1; 0.3)	0.295	0.77	1.03	0.311	-0.4 (-1.2; 0.3)	0.246	0.3 (-0.3; 0.9)	0.311
- BADL	0.70	317.31	<0.001	-0.5 (-0.8; -0.1)	0.008	0.70	1.86	0.173	-0.5 (-0.8; -0.2)	0.004	0.2 (-0.1; 0.4)	0.174
- IADL	0.73	370.19	<0.001	-0.1 (-0.7; 0.5)	0.727	0.73	0.00	0.986	-0.1 (-0.7; 0.5)	0.731	0 (-0.4; 0.4)	0.986
GP contact-time (minutes)[3]	0.56	112.64	<0.001	1 (-18; 20)	0.940	0.56	0.04	0.834	0 (-19; 20)	0.974	2 (-14; 17)	0.834
Hospitalization	0.08	30.54	<0.001	0.9 (0.7; 1.2)	0.521	0.08	0.02	0.886	0.9 (0.7; 1.2)	0.901	1.0 (0.8; 1.3)	0.886

1 Both models are adjusted for sex, age and baseline.

2 For the outcome 'Hospitalization' the Nagelkerke R^2 was used to estimate R^2.

3 GP contact information was available for 359 participants.

Predictive value of baseline handgrip and quadriceps strength on health outcomes at follow-up

The longitudinal analysis of the association between handgrip or quadriceps strength at baseline and health outcomes at year one is shown in Table 4. Handgrip strength was significantly associated with EQ5D+c (β= 0.05 [95% CI 0.02; 0.08]) and the BADL items of the GARS (β= -0.5 [95% CI -0.8; -0.2]) after one year of follow-up (adjusted for baseline, Model I). When quadriceps strength was included in the analysis, handgrip strength remained significantly associated with these parameters (Model II). Quadriceps strength was not significantly associated with EQ5D+c, GARS, GP contact-time or hospitalization at follow-up.

Characteristics and health outcomes among the different handgrip and quadriceps strength categories

Participants were grouped according to their handgrip and quadriceps strength status (weak or normal). Table 5 shows the characteristics and health outcomes of the four handgrip and quadriceps strength categories. Participants with weak handgrip and normal quadriceps strength ('weak handgrip strength only') were older (P <0.001) and had a lower body weight (P <0.001) in comparison to participants with normal handgrip strength and normal quadriceps strength ('normal handgrip and quadriceps strength'). The 'weak handgrip strength only' group scored more poorly on GARS (including IADL) and gait speed at baseline (all P <0.001). At follow-up, the 'weak handgrip strength only' group scored lower on EQ5D+c and BADL (all P ≤0.044).

Participants with weak quadriceps and normal handgrip strength ('weak quadriceps strength only') were older (P =0.007) and had a lower body weight (P =0.002) in comparison to the 'normal handgrip and quadriceps strength' group. With regard to the health outcomes, the 'weak quadriceps strength only' group scored more poorly on EQ5D+c, GARS (including both BADL and IADL) and gait speed at baseline (all P ≤0.001) when compared to the 'normal and quadriceps strength' group. Health outcomes measured at follow-up, however, did not differ significantly.

Participants scoring weak on both the handgrip and quadriceps strength ('weak handgrip and quadriceps strength') scored more poorly on all measured health parameters at baseline when compared to the 'normal handgrip and quadriceps strength', 'weak handgrip strength only' or the 'weak quadriceps strength only' groups (all P ≤0.034). The baseline characteristics of the 'weak handgrip and quadriceps strength' group differed most with the 'normal handgrip and quadriceps strength' group; participants were older, had more chronic diseases and a lower body weight (all P <0.001). When compared to the 'weak handgrip strength only' group, the 'weak handgrip and quadriceps strength' participants only differed in the number of chronic diseases (5 versus 4, P <0.001). In

Table 5. Health outcomes among the different handgrip and quadriceps strength categories.

	Normal handgrip and normal quadriceps strength (n=267)	Weak handgrip and normal quadriceps strength (n=134)		Normal handgrip and weak quadriceps strength (n=165)		Weak handgrip and weak quadriceps strength (n=198)	
	Median [IQR]	Median [IQR]	*P*-value[1]	Median [IQR]	*P*-value[1]	Median [IQR]	*P*-value[2]
Baseline characteristics							
Female[3]	184 (68.9)	90 (67.2)	0.723	117 (70.9)	0.662	130 (65.7)	0.776
Age (yr)	81 [78; 85]	84 [80; 88]	<0.001	82 [79; 86]	0.007	85 [80; 89]	0.165
N chronic diseases[4]	3 [2; 5]	4 [3; 5]	0.346	4 [2; 6]	0.193	5 [3; 6]	<0.001
Weight (kg)	76 [67; 84]	71 [61; 80]	<0.001	71 [62; 81]	0.002	69 [60; 80]	0.826
Health outcomes at baseline[5]							
EQ5D+c	0.81 [0.72; 0.89]	0.81 [0.69; 0.86]	0.948	0.81 [0.68; 0.84]	<0.001	0.68 [0.30; 0.81]	<0.001
GARS	25 [21; 31]	31 [25; 38]	<0.001	29 [24; 36]	<0.001	40 [32; 49]	<0.001
- BADL	9 [9; 10]	9 [9; 11]	0.141	9 [9; 11]	0.001	11 [9; 17]	<0.001
- IADL	16 [12; 21]	21 [16; 27]	<0.001	20 [15; 25]	<0.001	28 [22; 33]	<0.001
GP contact-time (minutes)[6]	100 [40; 170]	100 [43; 198]	0.753	90 [40; 170]	0.693	185 [103;368]	0.005
Hospitalization[3]	40 (15.0)	28 (21.1)	0.152	27 (16.4)	0.667	62 (31.6)	0.034
Gait speed (m/s)	0.67 [0.50; 0.84]	0.52 [0.36; 0.66]	<0.001	0.50 [0.31; 0.65]	<0.001	0.30 [0.05; 0.46]	<0.001
Health outcomes at follow-up[7]							
Mortality[3]	8 (3.0)	7 (5.2)	0.812	6 (3.6)	0.708	10 (5.1)	0.825
EQ5D+c	0.81 [0.69; 0.89]	0.73 [0.56; 0.84]	0.044	0.81 [0.65; 0.84]	0.954	0.65 [0.26; 0.81]	0.479
GARS	28 [22; 35]	35 [29; 43]	0.156	33 [25; 41]	0.995	43 [34; 51]	0.379
- BADL	9 [9; 11]	11 [9; 14]	0.017	10 [9; 12]	0.785	13 [10; 19]	0.819
- IADL	18 [13; 25]	24 [19; 29]	0.294	23 [16; 29]	0.870	30 [24; 35]	0.419
Hospitalization[3]	41 (19.6)	23 (23.5)	0.495	26 (20.3)	0.778	30 (21.7)	0.567
GP contact-time (minutes)[6]	100 [50; 170]	105 [53; 245]	0.706	120 [60; 240]	0.384	210 [73; 398]	0.697

1 Numbers were compared to the normal handgrip and normal quadriceps strength group using general linear model (GLM) univariate analysis.

2 Numbers were compared to the weak handgrip and normal quadriceps strength group using GLM univariate analysis.

3 Number (%).

4 Including self-reported diabetes, heart failure, cancer, chronic obstructive pulmonary disease, incontinence, arthritis, osteoporosis, dizziness, lower urinary tract symptoms, depression, anxiety, dementia, impaired vision, deafness, fracture, stroke/transient ischemic attack, myocardial infarction.

5 GLM univariate analyses were corrected for age and sex.

6 GP contact information was available for 359 participants; the numbers of participants analyzed in the respective groups are 134, 67, 79 and 79.

7 GLM univariate analyses were corrected for age, sex and health outcome at baseline. Follow-up information was available for 570 participants: the numbers of participants analyzed in the respective groups are 208, 98, 127 and 137.

comparison to the 'weak quadriceps strength only' group, the 'weak handgrip and quadriceps strength' participants had more chronic diseases and were older (all P <0.001).

At follow-up, the 'weak handgrip and quadriceps strength' group only scored lower on EQ5D+c when compared to the 'normal handgrip and quadriceps strength' and the 'weak quadriceps strength only' groups (all P ≤0.006). The health outcomes at follow-up did not differ between the 'weak handgrip and quadriceps strength' and the 'weak handgrip strength only' groups.

Following the frailty criteria by Fried et al.[20], 74.2% of the 'weak handgrip and quadriceps strength' group were considered frail compared to 38.8% in the 'weak handgrip strength only' group. In the 'normal handgrip and quadriceps strength' and 'weak quadriceps strength only' groups respectively 8.2% and 9.1% were considered frail.

DISCUSSION

We compared the lower limb quadriceps strength with the handgrip strength in their association with health outcomes in older adults in primary care. We showed that in an older population the association between quadriceps strength and handgrip strength is weak, and that quadriceps strength and handgrip strength are both independently associated with several health outcomes at baseline. Further, combined weakness of the quadriceps and handgrip identified a subpopulation of older adults that presents with the poorest health scores at baseline, as demonstrated by increased morbidity, lower quality of life, increased disability in daily living, increased GP contact, increased hospitalization and slower gait speed. This group of vulnerable older adults scored significantly poorer on all measured health parameters compared to those characterized by handgrip weakness only.

Prospectively, quadriceps strength showed no association with the measured health outcomes, whereas handgrip strength was associated with quality of life and BADL only. Quadriceps weakness did not contribute to the prediction of lower health scores, and handgrip weakness was sufficient to distinguish older adults with lower health, whom presented with a lower quality of life and decreased BADL.

In clinical practice, handgrip strength measurements are often preferred over lower limb muscle measurements in determining sarcopenia[3]. This has several reasons: first, measuring the handgrip strength is an easy, accessible and inexpensive method to use. In addition, handgrip strength has been reported to correlate well with a number of health parameters, as well as leg strength, which suggests an interchangeability of upper and lower limb muscle measurements[3, 13]. However, our data in a population of older adults did not show a strong correlation between handgrip and quadriceps strength. This discrepancy may be explained by the study population used, as our population

consisted of older adults aged 75 and above, whereas the previous study demonstrating a strong correlation between upper and lower limb muscle strength consisted of a study population with an age range from 20 to 102[13]. Older people progressively show more physical impairments, which may distort the correlation between upper and lower limb muscle strength.

In addition, we observed that both quadriceps strength and handgrip strength associated independently with several health outcomes at baseline. These health outcomes included disability in daily living and gait speed (mobility-related items) and quality of life. Surprisingly, the effect estimates of the quadriceps and handgrip strength were very comparable for disability in daily living, GP contact-time, hospitalization and gait speed, whereas quality of life showed a stronger association with quadriceps strength. Our prospective analysis showed an overall limited association with health outcomes. Handgrip strength was only associated with quality of life and BADL, and quadriceps strength was associated with none of the measured health outcomes.

When grouping the participants according to handgrip and quadriceps weakness, we observed that weakness in the handgrip strength contributed to poorer health scores at baseline and follow-up, whereas quadriceps weakness contributed only to poorer health scores at baseline. The lack of a strong correlation between handgrip and quadriceps strength, together with their independent associations with distinct health outcomes suggest that the two muscle parameters reflect different properties at old age. By measuring either handgrip strength or quadriceps strength vulnerable older adults can be identified, however, it is the combined use of both muscle parameters that distinguishes the most vulnerable subpopulation.

Strengths and limitations

Our study population consists of older adults who participated in the ISCOPE study. As this is a large population-based study with few exclusion criteria, it augments the external validity of our results, which is a strength of this study. In addition, we analyzed the association of the quadriceps and handgrip strength with respect to one another to distinguish their individual effects on health outcomes. Although previous studies have reported the association of quadriceps and handgrip strength with several negative health outcomes, none of these studies analyzed the association independent of the other muscle parameter[6, 7, 9-11]. A limitation of our study is the short follow-up period and the relatively small sample size, which may explain the lack of association between baseline quadriceps strength and health outcomes at follow-up.

Persons with complex problems were oversampled in our study, which could be considered a limitation as it may have resulted in the overestimation of negative health outcomes. However, handgrip and/or quadriceps weakness are likely to be similarly overestimated due to the oversampling. Oversampling may have affected the associa-

tion between handgrip and quadriceps strength, as health problems do not always equally affect handgrip strength and quadriceps strength. We addressed this matter by analyzing the effect of the individual muscle parameters independently of each other.

Implications

Our results confirm that handgrip weakness is a good parameter for the association and prediction of poor health status in the elderly as reported previously[4-7]. In addition, our study shows that handgrip weakness is not automatically linked to quadriceps weakness suggesting that measuring quadriceps strength next to handgrip strength may have added value in assessing sarcopenia more accurately. Measuring quadriceps strength aids in the assessment of poorer health status in older adults in primary care, as it helps to identify those older adults at increased risk of negative health outcomes. Although it has been suggested that lower limb muscle strength associates more strongly with health outcomes related to mobility[3], we did not observe a difference in the association of mobility-related health outcomes (e.g. gait speed and GARS) with handgrip strength or quadriceps strength. This suggests that other determinants such as balance may play a more significant role in mobility than previously hypothesized[3].

CONCLUSIONS

Our study shows that in an older population quadriceps strength and handgrip strength are only moderately associated, and that quadriceps strength and handgrip strength associate independently with several health outcomes. Although quadriceps strength measurements do not contribute to the prediction of adverse health outcomes, the combination of quadriceps strength measurements with handgrip strength measurements, may aid in the identification of older adults in primary care with the poorest health. These older people present with the poorest scores on quality of life, disability in daily living, GP contact-time, hospitalization and gait speed.

REFERENCES

1. Morley JE, Baumgartner RN, Roubenoff R, Mayer J, Nair KS. Sarcopenia. J Lab Clin Med 2001;137(4):231-243.
2. Rolland Y, Czerwinski S, Abellan Van KG et al. Sarcopenia: its assessment, etiology, pathogenesis, consequences and future perspectives. J Nutr Health Aging 2008;12(7):433-450.
3. Cruz-Jentoft AJ, Baeyens JP, Bauer JM et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing 2010;39(4):412-423.
4. Femia EE, Zarit SH, Johansson B. Predicting change in activities of daily living: a longitudinal study of the oldest old in Sweden. J Gerontol B Psychol Sci Soc Sci 1997;52(6):294-302.
5. Giampaoli S, Ferrucci L, Cecchi F et al. Hand-grip strength predicts incident disability in non-disabled older men. Age Ageing 1999;28(3):283-288.
6. Hairi NN, Cumming RG, Naganathan V et al. Loss of muscle strength, mass (sarcopenia), and quality (specific force) and its relationship with functional limitation and physical disability: the Concord Health and Ageing in Men Project. J Am Geriatr Soc 2010;58(11):2055-2062.
7. Rantanen T, Era P, Heikkinen E. Maximal isometric strength and mobility among 75-year-old men and women. Age Ageing 1994;23(2):132-137.
8. Rantanen T, Masaki K, Foley D, Izmirlian G, White L, Guralnik JM. Grip strength changes over 27 yr in Japanese-American men. J Appl Physiol 1998;85(6):2047-2053.
9. Cawthon PM, Fox KM, Gandra SR et al. Do muscle mass, muscle density, strength, and physical function similarly influence risk of hospitalization in older adults? J Am Geriatr Soc 2009;57(8):1411-1419.
10. Laukkanen P, Heikkinen E, Kauppinen M. Muscle strength and mobility as predictors of survival in 75-84-year-old people. Age Ageing 1995;24(6):468-473.
11. Newman AB, Kupelian V, Visser M et al. Strength, but not muscle mass, is associated with mortality in the health, aging and body composition study cohort. J Gerontol A Biol Sci Med Sci 2006;61(1):72-77.
12. Rantanen T, Volpato S, Ferrucci L, Heikkinen E, Fried LP, Guralnik JM. Handgrip strength and cause-specific and total mortality in older disabled women: exploring the mechanism. J Am Geriatr Soc 2003;51(5):636-641.
13. Lauretani F, Russo CR, Bandinelli S et al. Age-associated changes in skeletal muscles and their effect on mobility: an operational diagnosis of sarcopenia. J Appl Physiol 2003;95(5):1851-1860.
14. Rantanen T, Guralnik JM, Ferrucci L et al. Coimpairments as predictors of severe walking disability in older women. J Am Geriatr Soc 2001;49(1):21-27.
15. Visser M, Goodpaster BH, Kritchevsky SB et al. Muscle mass, muscle strength, and muscle fat infiltration as predictors of incident mobility limitations in well-functioning older persons. J Gerontol A Biol Sci Med Sci 2005;60(3):324-333.
16. Poot AJ, den Elzen WP, Blom JW, Gussekloo J. Level of satisfaction of older persons with their general practitioner and practice: role of complexity of health problems. PLoS One 2014;9(4):e94326.
17. Hanten WP, Chen WY, Austin AA et al. Maximum grip strength in normal subjects from 20 to 64 years of age. J Hand Ther 1999;12(3):193-200.
18. Ling CH, Taekema D, de Craen AJ, Gussekloo J, Westendorp RG, Maier AB. Handgrip strength and mortality in the oldest old population: the Leiden 85-plus study. CMAJ 2010;182(5):429-435.

19. Taekema DG, Gussekloo J, Maier AB, Westendorp RG, de Craen AJ. Handgrip strength as a predictor of functional, psychological and social health. A prospective population-based study among the oldest old. Age Ageing 2010;39(3):331-337.
20. Fried LP, Tangen CM, Walston J et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56(3):M146-M156.
21. Andrews AW, Thomas MW, Bohannon RW. Normative values for isometric muscle force measurements obtained with hand-held dynamometers. Phys Ther 1996;76(3):248-259.
22. Stark T, Walker B, Phillips JK, Fejer R, Beck R. Hand-held dynamometry correlation with the gold standard isokinetic dynamometry: a systematic review. PM R 2011;3(5):472-479.
23. Douma RK, Soer R, Krijnen WP, Reneman M, van der Schans CP. Reference values for isometric muscle force among workers for the Netherlands: a comparison of reference values. BMC Sports Sci Med Rehabil 2014;6(1):10.
24. Kwoh CK, Petrick MA, Munin MC. Inter-rater reliability for function and strength measurements in the acute care hospital after elective hip and knee arthroplasty. Arthritis Care Res 1997;10(2):128-134.
25. Schaubert KL, Bohannon RW. Reliability and validity of three strength measures obtained from community-dwelling elderly persons. J Strength Cond Res 2005;19(3):717-720.
26. EuroQol Group. EuroQol—a new facility for the measurement of health-related quality of life. The EuroQol Group. Health Policy 1990;16(3):199-208.
27. Krabbe PF, Stouthard ME, Essink-Bot ML, Bonsel GJ. The effect of adding a cognitive dimension to the EuroQol multiattribute health-status classification system. J Clin Epidemiol 1999;52(4):293-301.
28. Cantril H. The Pattern of Human Concerns. Rutgers University Press; 1966.
29. Kempen GI, Miedema I, Ormel J, Molenaar W. The assessment of disability with the Groningen Activity Restriction Scale. Conceptual framework and psychometric properties. Soc Sci Med 1996;43(11):1601-1610.
30. Bootsma-van der Wiel A, Gussekloo J, de Craen AJ et al. Disability in the oldest old: "can do" or "do do"? J Am Geriatr Soc 2001;49(7):909-914.
31. Bloem BR, Haan J, Lagaay AM, van BW, Wintzen AR, Roos RA. Investigation of gait in elderly subjects over 88 years of age. J Geriatr Psychiatry Neurol 1992;5(2):78-84.
32. van Houwelingen AH, den Elzen WP, Mooijaart SP et al. Predictive value of a profile of routine blood measurements on mortality in older persons in the general population: the Leiden 85-plus Study. PLoS One 2013;8(3):e58050.





EFFECTIVENESS AND COST-EFFECTIVENESS OF A PROACTIVE, GOAL-ORIENTED, INTEGRATED CARE MODEL IN GENERAL PRACTICE FOR OLDER PEOPLE. A CLUSTER RANDOMIZED CONTROLLED TRIAL: INTEGRATED SYSTEMATIC CARE FOR OLDER PEOPLE - THE ISCOPE STUDY

Jeanet W. Blom, Wendy P.J. den Elzen & Anne H. van Houwelingen,
Margot Heijmans, Theo Stijnen, Wilbert B. van den Hout and Jacobijn Gussekloo

Submitted

ABSTRACT

Background

Older people often experience a combination of somatic, functional, mental and/or social problems (complex problems). These problems are not always known to care providers. The general practitioner (GP) usually only acts on demand. For vulnerable older people, screening/monitoring of complex problems and a proactive way of working is important, although not common in primary care. Because of multiple problems, care for older people in general practice needs to shift from a vertical disease-oriented care aiming at improvement of outcomes per disease, to a horizontal problem-based, goal-oriented care, integrating all health care providers. The feasibility and cost-effectiveness of this pro-active and integrated way of working is not yet established.

Methods

Design: Cluster randomized trial.

Participants: all persons aged ≥75 years in 59 general practices (30 intervention, 29 control), with a combination of problems, as identified with a structured postal questionnaire with 21 questions on 4 health domains.

Intervention: for participants with problems on ≥3 domains general practitioners (GPs) made an integrated care plan using a functional geriatric approach. Control practices: care as usual. Outcome measures: i) quality of life (QoL), ii) activities of daily living, iii) satisfaction with delivered healthcare and iv) cost-effectiveness of the intervention, at 1-year follow-up.

Trial registration: Netherlands trial register, NTR1946.

Results

Of the 11,476 registered eligible older persons, 7285 (63%) participated in the screening. 1921 (26%) had problems on ≥3 health domains. For 225 randomly chosen persons a care plan was made. No beneficial effects were found on QoL, patients' functioning or healthcare use/costs. GPs experienced better overview of the care and stability, eg. less unexpected demands, in the care.

Conclusions

GPs prefer proactive integrated care. 'Horizontal' care using care plans for older people with complex problems can be a valuable tool in general practice. However, no direct beneficial effect was found for older persons.

INTRODUCTION

With the aging population an ever-increasing number of older people with multiple health problems will be depending on health care. In recent decades health care has tended to be organized by means of vertical, disease-oriented programs. However, one disease and/or its intervention could influence the diagnosis, impact or treatment of another disease. These interactions between diseases and their treatment complicate the determination of disease-specific treatment goals. Thus, for older persons with multiple health problems, this model does not suffice[1,2].

In these older patients, illness presentation and the consequences of disease is better clarified with integrative disease models rather than by simple medical models[1]. Since wellbeing and providing for oneself without assistance from others is of increasing importance for older patients with multiple health problems[3], care for older people needs to shift from vertical disease-oriented care aiming at improvement of outcomes per disease, to problem-based, goal-oriented care. Therefore, an integrated, horizontal care model aiming at global health outcomes is more suitable than a vertical model mainly aiming at improving disease outcomes[4]. The problems older people are facing are not always known to care providers. The general practitioner (GP) may sometimes suspect the presence of some of these problems, but usually only acts on demand. Therefore, this model of care should be provided in a proactive way in order to set and prioritize goals together with the patient and to empower the patient to reach these goals.

Although this shift from vertical care to horizontal care sounds ideal in theory, actual implementation in primary care can be difficult. Models that have been investigated, range from light interventions to intensive guided care[5-7]. However, until now, no important positive effects have been shown. Also, although some studies examined cost savings, to our knowledge few studies have evaluated cost-effectiveness.

The ISCOPE (Integrated Systematic Care for Older PEople) study aims to assess the effectiveness and cost-effectiveness of a simple structural monitoring system to detect the deterioration in somatic, functional, mental or social health of individuals aged 75 years and over followed by the execution of a care plan for those people with a combination of somatic, functional, mental and social problems. The ISCOPE study operationalizes horizontal care by developing a care plan for older persons with complex problems, i.e. a combination of functional, somatic (health and illness), mental and/or social problems[8]. The care plan focuses on function rather than on disease and aims to restore, maintain or maximize functional independence, or to compensate for loss of autonomy by appropriate support (functional approach). Although the approach is functional, underlying disease can still be a focus of attention. The goals, wishes and expectations of the older person are the starting point for the care plan[9]. To identify older persons with complex problems pro-actively, the ISCOPE study uses a simple structural screening and moni-

toring system to detect deterioration in somatic, functional, mental or social health of individuals aged ≥ 75 years, and brings this to the attention of the general practitioner (GP).

MATERIALS AND METHODS

Design Overview

The study is an observer-blinded cluster randomized-controlled trial with randomization at the level of the general practice. To avoid contamination we used a complete consent pre-randomization design[10,11]. The Medical Ethical Committee of the Leiden University Medical Center approved the study. The study was registered in the Netherlands Trial Register (NTR1946).

Setting and Participants

Recruitment of general practices

All 560 GPs in the region of Leiden, the Netherlands, were invited to participate. In the initial invitation letter, we provided as little information as possible about the intervention to prevent behavioral change in the control group of GPs[12]. Before inviting the older people to participate, we asked GPs to classify all enlisted older people into three categories according to their own perception: i) not vulnerable, ii) possibly vulnerable, and iii) vulnerable.

Recruitment of participants

In the Netherlands all community-dwelling persons are registered at a GP. During the inclusion period (September 2009 to September 2010) all persons aged ≥ 75 years received an invitation by mail from their GP to participate in the study. The GPs excluded people with terminal illness or an expected life expectancy of ≤ 3 months. Also included with this invitation were a screening questionnaire (Appendix 1) addressing four domains of health and an informed consent form. All older people who participated in the screening provided written informed consent. After 3 weeks the non-responders were contacted again by telephone and, if required, were assisted by telephone or visited at home to fill in the screening questionnaire. A total of 7285 older persons responded by sending in the complete screening questionnaire (Figure 1).

Randomization and Interventions

Training of GPs

After randomization (after screening), the GPs and practice nurses of the intervention practices were trained (during 2 sessions of 3 hours each) by a GP specialized in geriatric care to deliver pro-active integrated care, including designing, conducting and adjusting a care plan (Appendix 3). During the intervention the GPs had the possibility to consult a GP with special post-graduate training in geriatrics and they received an extra training of three hours on resources and organization of care to older people in primary care.

Screening questionnaire

The screening questionnaire contained questions on four domains of health: functional, somatic (health and illness), mental and social and each domain contained 4-9 questions. [8] A positive answer to two or more questions in a domain led to a positive score on the domain. The questions were derived from existing validated questionnaires[13-14] and were based on predictors related to functional decline[15-19]. Individuals with problems on three or four domains were classified as having complex problems which is associated with poor outcomes on disability, feelings of loneliness, health related quality of life and GP contact time[8]. In the intervention practices, the GPs received the results of the screening questionnaire of their own patients. In the control practices, GPs did not receive feedback about the screening questionnaire and provided care as usual to their older patients.

Care plan

In the intervention practices, the GP or the practice nurse (under supervision of the GP) made an integrated care plan for participants with complex problems. This care plan consisted of two steps. The first was an inventory of the existing health problems using problem areas as introduced by Bangma, stemming from Dutch rehabilitation medicine: somatic, activities of daily living, social, mental and communicative problems[20]. The wishes and expectations of the older person about goals to be achieved were explored in a dialogue with the participant and informal caregiver(s). Subsequently, a care plan was made, taking the priorities and goals of the older person and informal caregiver as a starting point (Appendix 4). The GP/practice nurse, together with the older person, formulated actions to be taken and evaluation plans for follow-up. Other care professionals were involved where needed (multidisciplinary consultation). For the purpose of the present study, the participating GPs made care plans for a maximum of 10 randomly chosen participants with complex problems. For the participants with complex problems who were not selected usual care was provided. These participants were not included in the final analysis.

Outcomes and Follow-up

At baseline and at 1-year follow-up participants were visited by a research nurse to measure outcomes. At 6 months post-baseline the EQ-5D was sent by mail.

To show the outcome of the screening a comparison was made between participants with complex problems and participants without complex problems with data from the EPR and data from the questionnaires.

Primary outcome

The primary outcomes was quality of life at 1-year follow-up as measured with Cantril's ladder[21], and competence in basic activities of daily living (BADL) and instrumental activities of daily living (IADL) at 1-year follow-up as measured with the Groningen Activities Restriction Scale (GARS)[22], and. Quality of life was measured by Cantril's ladder that has steps ranging from 0 to 10[23]. The GARS is a questionnaire that assesses disabilities in competence in 9 BADL items and 9 IADL items. (range 18-72, higher score means more disability).

Secondary outcomes

Because we used a comprehensive intervention we used a wide array of secondary outcomes.

As secondary outcomes we examined satisfaction with delivered care of the older persons, the GPs and informal caregivers[24].

Older people: Participants were asked to indicate their satisfaction with and confidence in their GP, pharmacist, specialist, physiotherapist, hospital and home care on a 5-point Likert scale. The 5 levels of satisfaction were then dichotomized into 'satisfied' (including very satisfied, satisfied and neutral) and 'dissatisfied' (including dissatisfied and very dissatisfied)[25]. Answers to the questions regarding confidence were dichotomized in the same way.

General practitioners: At baseline and at 1-year follow-up, questionnaires were sent to GPs in the intervention group asking them about the overview of care needs, stability in the care situation, and (expected) improvement in the care situation for each participant for whom they had made a care plan (answers on a 10-point scale). To evaluate the experiences of the GPs with the screening and care plans, two focus groups were organized (each with four GPs). In both groups, three GPs had extra staff available to enable them to place more focus on the care of their older patients. The first group consisted of GPs who did not manage or only partly managed to complete care plans, and the second group consisted of GPs who completed all the care plans.

Informal caregivers: At baseline and at 1-year follow-up, informal caregivers were sent a questionnaire about the amount of time spent on care for the older participant (hours per week spent on household activities, personal care, and activities outside the house), the burden of this care (score 0-10) and their quality of life (score 0-10)[24].

Other secondary outcomes

Cognitive function was measured with the Mini-Mental State Examination (MMSE) with scores ranging from 0-30 points (higher score means less cognitive problems)[26]. Depressive symptoms were assessed with the 15-item Geriatric Depression Scale (GDS-15), with scores ranging from 0 (optimal) to 15 (higher score means more depression)[27]. The GDS-15 was administered only to participants with an MMSE score ≥ 18 points. Self-rated health was measured using the question 'How do you rate your health in general?' on a 5-point scale ranging from 1 to 5, and the question 'How do you rate your health compared to one year ago?' on a 5-point scale ranging from 1 to 5. Self-rated loneliness was assessed with the Loneliness Scale of De Jong Gierveld (DJG) an 11-item questionnaire covering both emotional loneliness (6 items) and social loneliness (5 items) that was specifically developed for use in elderly populations (higher score means more social problems)[28].

Since the study was aimed at identifying older people with complex problems, we also evaluated combined outcomes indicating complexity. We used the total score on the ISCOPE screening questionnaire and a combined Z score of the GARS score (functional domain), self-rated health (somatic domain), GDS score (mental domain), and DJG score (social domain).

Process evaluation and contents of the care plan

The content of the care plans is described by the median number of defined problems, goals and actions (with interquartile range; IQR), the percentage of problems, goals and actions, and the 'level' of functional approach used in the description of the problem-goal-action sequence: handicap/limitation, complaint/symptom, disease/diagnosis, other. To categorize the problems, type of goals and type of actions we used a partly deductive (start with predefined categories based on anatomic areas for the problems) and partly inductive (include extra categories) process.

Sample size

The required sample size was based on the change in BADL. In the Leiden 85-plus Study we found a decrease of ~1.4 points per year, with a standard deviation (SD) of 3[18, 28]. Based on this result we decided on a change of 1.0 point as a clinically relevant difference. With a power of 85%, a significance level of 0.05 we needed a sample size of 163 patients per group (IBM SPSS Sample Power 3). To take cluster randomisation into account we used

the following formula: ESS = mk / (1+ ICC(m-1)) with m = number of vulnerable elderly of 75 years and older in a general practice, k = number of practices, ESS = "effective sample size" as calculated as if we use randomization on a patient level[30]. Assuming that about 10 participants with complex problems would be feasible per general practice, an intra-cluster correlation coefficient (ICC) of 0.05[30], and also taking dropout into account, it was estimated that about 60 general practices should be recruited.

Analysis non-response screening

To compare responders (with and without complex problems) and non-responders, we used patient data from a rural and a city GP practice (total of 629 patients) who participated in the ISCOPE study. Anonymous data from the electronic patient records (EPR) were available for participants and non-participants. A comparison was made of socio-demographic data, diseases (International Classification of Primary Care (ICPC) codes), medication, use of care, and the GP's appraisal of vulnerability. For each health domain, corresponding items in the EPR were compared (e.g. for the functional domain the number of home visits and number of referrals to physiotherapy were compared, and for the somatic domain the number of prevalent diseases (ICPC-codes) was compared).

Statistical Analysis

Descriptive statistics were used to compare baseline characteristics of the participants in the intervention and control practices. Means and SD are used for continuous variables that were normally distributed and medians with IQR for continuous variables that were not normally distributed. Proportions are used to describe differences in categorical variables. In both groups, mortality differences between participants with complex problems were analyzed using Cox regression analysis. Differences in median scores between baseline and follow-up in the GP questionnaire were tested with Mann-Whitney U-tests, because incomplete scoring in the GP questionnaires prevented a paired analysis,

The primary analysis focused on the difference in Cantril's ladder score and ADL score (GARS BADL and IADL) between participants with complex problems for whom a care plan should have been made (intervention group) compared with all participants with complex problems in the care as usual practices (control group).

Analyses were performed on an intention-to-treat basis and per protocol basis. A sensitivity analysis for effectiveness was performed in the group of participants with problems in 4 domains. A linear mixed model (LMM) analysis was used, correcting for age, sex, baseline scores and clustering of patients per general practice. The model included a variable for time of measurement (baseline and 1-year follow-up) and a variable for allocation (with value 0 in control patients and value 1 at 1 year follow-up in intervention group patients). The estimate for time of measurement shows the change

in score for the control group. The estimate for the allocation shows the difference in change in score between the intervention and control group. Because we assumed that the intervention would have no effect on mortality (which was confirmed by the analysis on mortality) and we were exploring the effect in those that survived, participants who died during follow-up were excluded from the primary outcome analyses. The LMM analysis corrects for outcomes missing at random.

Analysis of focus groups

Focus group interviews were recorded and transcribed verbatim. We used thematic analysis involving coding, categorizing and theme identification. All incentives and barriers for screening and care plans mentioned in the verbatim reports were coded and analysed independently by two researchers (JWB, WdE).

Economic evaluation

The cost-effectiveness of the intervention from a societal perspective during the 1-year follow-up was analyzed (Appendix 5).

Role of the funding source

This study was funded by ZonMw, the Netherlands, Organization for Health Research and Development: ZonMw No. 311060201. The sponsor had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

RESULTS

Participants

General practitioners

Of the 560 GPs approached, 104 (19%) working in 59 general practices agreed to participate. Concern about the workload was the main reason for non-participation (28%); also, 4% had just left the practice, 4% had very few older people enlisted, 7% were not interested in the project, and 4% already implemented an intervention in the care for their older patients. The remaining practices had other reasons for non-participation or did not respond (34%).

The participating practices were representative for the urbanized area in the vicinity of the city of Leiden (the Netherlands).

Older people

The participation of older persons is shown in Figure 1. Of the 12,066 registered people aged ≥ 75 years, 590 (5%) were not eligible because they were deceased (0.9%), too ill (1.4%), admitted to a nursing home (1.1%), non-Dutch speaking (0.3%), or for other reasons (1.1%).

Screening

Of the 11,476 registered eligible older persons, 7285 (63%) participated in the screening and 4191 (37%) declined or did not respond for other reasons. One third of the population (2240, 31%) was assisted by a relative (n=1396, 19%) or a research nurse (n=844, 12%).

Non-response analysis

Non-responders are older and less often male than non-complex responders and do not differ in age and sex from complex responders (Table 1). Non-responders have the same number of disease and prescriptions but are more vulnerable according to the GP than non-complex responders. However, complex responders still have more disease and prescriptions, and are more vulnerable according to GP than both other groups.

Health care use in non-responders is similar to non-complex responders. Non-responders have less home visits. Complex responders have more GP consultations, GP home visits, physiotherapy and primary mental health care than both other groups.

Screening results

Table 2 shows the characteristics and screening results of participants who returned the screening questionnaire in the 30 intervention practices and of participants in the 29 control practices. Median age, sex, income, living circumstances and outcomes of the screening questionnaire were similar. Overall, 26% of the participants had complex problems. Participants with complex problems have a poorer score on all questionnaire outcomes compared to participants without complex problems (see additional table 1).

Participants with complex problems

Non-response analysis of participants with complex problems

For the baseline outcome measurement there were no significant differences in sex and reasons for non-participation between non-participants in the intervention group and non-participants in the control group (Additional figure 1; p-values see additional table 2). The median age of the non-participants in the control group was higher than that in the intervention group (84.2 vs 82.5 years; p=0.038); for the follow up outcome measurement this was 83.1 vs 84.1; p=0.536.

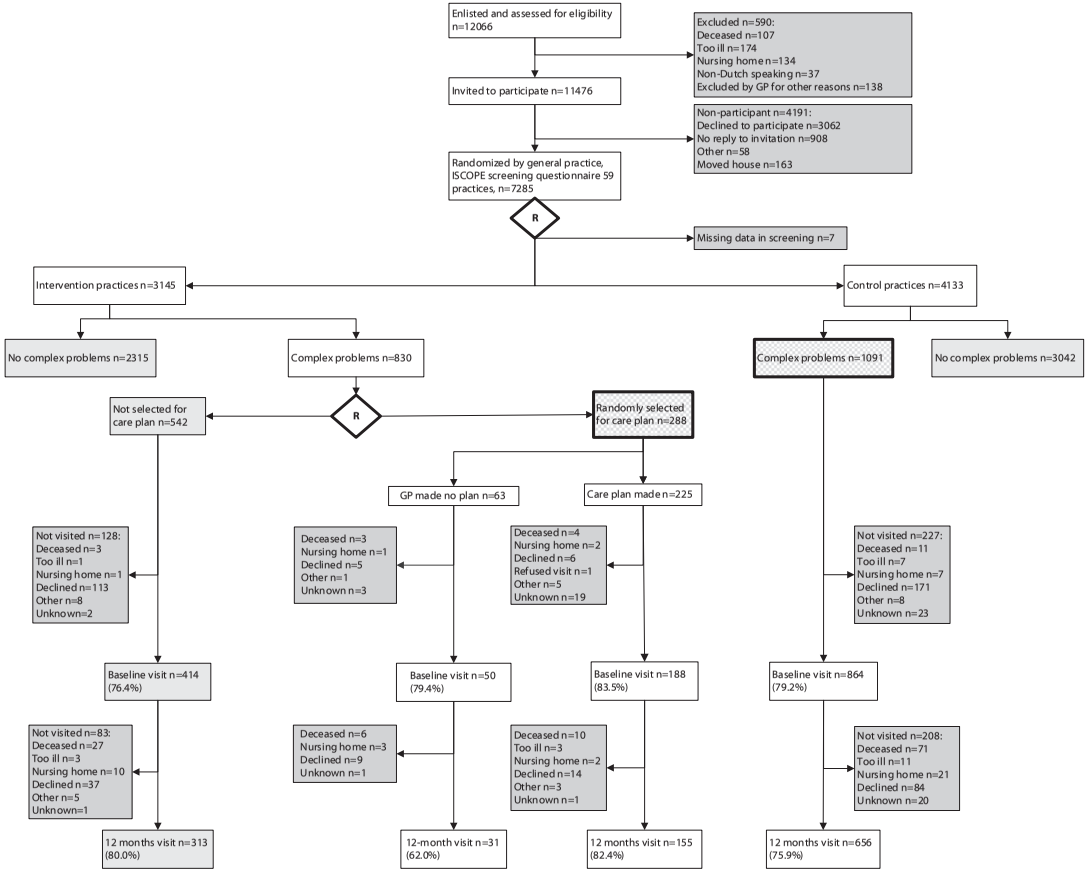


Figure 1. Flowchart of participants in the study.
The dotted grey squares indicate the two groups compared in the intention-to treat analysis

Table 1. Non-response in screening

		Responders				
	Total N=358	No complex problems N=280	Complex problems* N=75	Non-responder N=271	p-value non-responder vs non-complex responders	p-value non-responder vs complex responders
Age (median, IQR)	80 (77-83)	79 (77-82)	83 (78-86)	81 (78-85)	<0.001	0.103
Male sex (%)	42.3	46.1	28.0	33.9	0.004	0.331
Living alone (%)	20.0	17.8	28.0	24.4	0.059	0.530
Number of diseases (median, IQR)	2 (1-3)	2 (1-3)	3 (2-5)	2 (1-4)	0.045	<0.001
Vulnerable according to GP (%)	19.8	13.7	42.7	25.4	0.001	0.004
Number of prescriptions (median, IQR)	9 (5-13)	8 (4-12)	13 (8-19)	8 (4-12)	0.946	<0.001
Health care use last year						
Consultations GP (median, IQR)	8 (4-12)	7 (4-11)	12 (6-17)	7 (4-12)	0.486	<0.001
Home visits GP last year, yes/no (%)	36.9	29.3	65.3	44.6	<0.001	0.002
Out of hours contact GP, yes/no (%)	13.0	10.7	21.3	14.8	0.154	0.171
Referrals (median, IQR)	1 (0-3)	1 (0-2)	2 (1-4)	1 (0-2)	0.734	<0.001
Physiotherapy, yes/no (%)	15.5	13.2	24.0	9.2	0.138	0.001
Mental health care, yes/no (%)	1.9	2.6	0.0	3.4	0.671	0.132

*3 missing values

Table 2. Characteristics and screening results of participants who returned the screening questionnaire.

	Intervention group (30 practices) n=3145	Control group (29 practices) n=4133
Age in years: median (IQR)	80.5 (77.7; 84.5)	81.3 (77.9; 85.8)
Sex (female)	1913 (60.9)	2551 (61.7)
Only state pension	209 (15.4)	266 (15.0)
Living alone	698 (51.4)	1001 (56.4)
Complex problems	830 (26.5)	1091 (26.4)
≥2 problems in the domain		
Functional domain	785 (25.0)	1012 (24.6)
Somatic domain	1648 (52.7)	2124 (51.8)
Mental domain	1411 (45.0)	1906 (46.2)
Social domain	1040 (33.2)	1362 (33.0)

N (%) unless stated otherwise

Comparison of outcomes between intervention and control groups

Intra-cluster correlation coefficient

After analysis of the data we found an ICC of 0.002. Post hoc, a power of 85% was calculated for this study.

Patient outcomes

In total 288 participants with complex problems were randomly selected for a care plan out of the intervention practices. Table 3 shows the characteristics of the participants with complex problems in the intervention and control practices. Participants in the intervention practices selected for a care plan (n=288) were similar to those who were not selected for a care plan (Table 3).

During the 1-year follow-up, 19 (6.6%) participants in the intervention group and 87 (8.0%) in the control group died (p=0.479).

Table 4 presents the primary and secondary outcomes for the intention-to-treat analysis. In the control group the change in GARS score at 1-year follow-up (3.5; 95% confidence interval (CI): 3.0; 4.0) shows that this group is deteriorating rapidly. There was no difference in change in the score on Cantril's ladder or GARS score (total, BADL or IADL) between participants who were randomized to have a care plan made in the intervention group and participants with complex problems in the control group. Also, there was no difference in secondary patient outcomes. In a per-protocol analysis, i.e. in

Table 3. Baseline characteristics of participants with complex problems.

	Intervention group		Control group
	Not selected for care plan n=542	Selected for care plan n=288	n=1091
Age in years*	82.7 (79.2;87.1)	82.0 (78.8;86.9)	83.7 (79.8;88.0)
Sex (% female)	374 (69.0)	208 (72.5)	788 (72.2)
Score on four domains of screening questionnaire (%)	189 (34.9)	92 (31.9)	359 (32.9)
>4 medications (%)	423 (78.2)	233 (80.9)	808 (74.1)
GARS total score*	37 (29;47)	36 (27;45)	37 (29;46)
BADL subscale score*	11 (9;15)	11 (9;15)	11 (9;15)
IADL subscale score*	19 (25;33)	18 (25;30)	20 (26;32)
Cantril's ladder*	7 (6-8)	7 (6-8)	7 (6-8)
MMSE score*	27 (25;29)	28 (26;29)	27 (25;29)
GDS score*	3 (1;5)	2 (1;4)	3 (1;5)
DJG score*	4 (1;6)	3 (1;5)	4 (1;6)

*(median, IQR)

GARS	Groningen Activity Restriction Scale
BADL	Basic Activities of Daily Living
IADL	Instrumental Activities of Daily Living
MMSE	Mini Mental State Examination
GDS	Geriatric Depression scale
DJG	De Jong-Gierveld Loneliness scale

Table 4. Outcomes of the intention-to-treat analysis adjusted for age at screening, sex and baseline score.

Outcome	Change in 1-year follow-up for control group (n=1091)	p-value	Extra change in intervention group compared to control group (n=288)	p-value
Primary outcomes				
GARS total score	3.5 (3.0; 4.0)	<0.001	-0.6 (-1.7; 0.5)	0.299
GARS-subscale BADL	1.4 (1.1; 1.7)	<0.001	-0.2 (-0.9; 0.4)	0.450
GARS-subscale IADL	2.1 (1.8; 2.4)	<0.001	-0.4 (-1.1; 0.3)	0.238
Cantril's ladder	-0.2 (-0.3; 0.0)	0.004	0.0 (-0.2; 0.2)	0.823
Secondary outcomes				
MMSE	-0.7 (-1.0;-0.5)	<0.001	0.4 (0.0;0.9)	0.066
GDS-15	0.1 (-0.1;0.3)	0.168	0.0 (-0.4;0.4)	0.916
DJG	-0.1 (-0.3;0.1)	0.410	-0.1 (-0.5;0.3)	0.661
Total score ISCOPE screening	-0.6 (-0.8;-0.4)	<0.001	-0.3 (-0.8;0.1)	0.141
Combined outcome (Z scores)	-0.5 (-0.6;-0.4)	<0.001	0.0 (-0.3;0.3)	0.845

the intervention group only including participants for whom a care plan was made, no difference was found between the two groups (data not shown). A sensitivity analysis in participants with problems in 4 domains showed similar results.

Satisfaction with care

Older people's satisfaction with care

During the 1-year follow-up, the number of people satisfied with the GP increased in the intervention group (from 96.8% to 97.8%) and decreased in the control group (from 94.5% to 93.7%). No difference between the two groups was observed on confidence in the GP, or on satisfaction with and confidence in the other care providers.

GPs' satisfaction with care

GPs returned baseline questionnaires for 202 participants with a care plan and returned 1-year follow-up questionnaires for 146 of these participants. GPs reported an improvement in the overview of care needs [from median 7.0 (IQR 6.0-8.0) to 8.0 (IQR 7.0-9.0); $p<0.001$] and experienced more stability in the care situation [from median 7.0 (IQR 6.0-8.0) to 8.0 (IQR 7.0-8.0); $p<0.001$]. Although baseline expectations for improvement in the care situation were low, the reported actually experienced improvement at 1-year follow-up was good [median 5.5 (IQR 2.0-7.0) and 7.0 (IQR 6.0-8.0), respectively; $p<0.001$].

In the focus groups the GPs felt that new information had emerged from the screening, indicating (in particular) their possible 'blind spot' for mental and social issues. Some GPs feared that 'medicalization' was stimulated by the screening. GPs experienced more control over the care situation and were more aware of the functioning and wishes of the older people. However, they found the protocolised way of working difficult and suggested that it was perhaps more suited to the practice nurse. Some GPs preferred to focus on the medical task. Organising multidisciplinary consultations was found to be cumbersome.

Informal caregivers

Of the 269 responding informal caregivers (40 in the intervention group, 143 in the control group), the majority were children of the older person (60% and 59%, respectively); their median age was 61 (IQR 51-70) years and 62 (IQR 56-75) years, respectively; and in the intervention group 35% was male compared with 28% in the control group. The intervention group spent a median number of 5 (IQR 2-20) hours per week on household activities, 3 (2-14) on personal care and 4 (2-6) hours on outside activities. For the control group this was 5 (IQR 3-12), 3 (IQR 1-10) and 3 (IQR 1-7) respectively. Between baseline and 1-year follow-up there was no significant difference between the groups in the

(change in) time spent on care for the older participant, the burden felt by the informal caregiver, and their quality of life (see additional table 3).

Process evaluation and content of care plan

A total of 288 randomly chosen participants with complex problems were assigned to receive a care plan. Of these, in 7% (n=20) the GP indicated that the drafted care plan was not carried out due to death, referral to a nursing home, moving house, etc. In 15% (n=43) the GP did not prepare the care plan due to time constraints or other logistic problems. Three GPs did not manage to make any care plan at all. The median number of problems, goals and actions in the care plans was 3 (IQR 2-4), 4 (2-5) and 3 (2-5), respectively. The five most prevalent problems were: depressive complaints (20% of patients), loneliness/isolation (19%), decreased mobility (19%), memory complaints (17%), and hearing complaints (12%). The five most prevalent actions were: action by the patient or informal caregiver (13% of actions), such as engaging in social activities, referral to another physician (9%), further diagnostic interventions (9%), frequent check-up by the GP (7%), and optimizing the medication (7%). In the problem-goal-action sequences, 46% of descriptions were expressed as handicap/limitation, 46% as complaint/symptom and 8% as disease/diagnosis.

Economic evaluation

Costs were estimated at €236 per care plan (Appendix 5), which includes training of GPs and practice nurses (16%), screening (21%), making the care plan (30%) and carrying out the care plan (34%). These care plan costs constituted only 1.3% of the total healthcare costs during the 1-year follow-up. No differences were found in the use of other types of healthcare or in total health care costs.

DISCUSSION

This study evaluated a proactive horizontal approach by the GP for older patients, consisting of a brief (postal) screening questionnaire and making an integrated care plan for (some) patients with complex problems. The GPs had successfully taken on the functional approach, as seen from the contents of the care plans. GPs experienced better overview of care needs and more stability, eg less unexpected care demands, in the care for individual patients with complex problems. Older patients with complex problems were already largely satisfied with the care offered by their GP and the change in satisfaction was therefore small. Nevertheless, no significant improvement was found in quality of life or functional status after 1-year follow-up in participants with complex problems in the intervention group compared with those in the usual care group. In

addition, there was no significant difference in change of somatic problems and mental/social functioning, or in complexity. Except for the care plans, patients in the intervention group had the same amount of healthcare use and costs as the control group.

Comparison with literature

Two systematic reviews evaluated studies on complex interventions (with individualized assessment and provision, or referral to appropriate care) to prevent functional decline in older people[5,6]. Although one review showed a reduction in admissions to hospitals/nursing homes, a reduction in falls, and an improvement in functioning, the effects were only modest[5]. Moreover, the effects were mainly in studies conducted before 1993, suggesting that modification of care after 1993 was of little additional value; this idea has recently been confirmed[31]. The more recent review showed small effects on functioning, but mainly in studies performed in the US and not in non-US countries[6]. This latter review showed no effects on hospitalization, institutionalization or mortality; in addition, due to significant heterogeneity between the reviewed studies, the net benefit could not be determined[6]. Two other systematic reviews on comprehensive care programs for people with multi-morbidity were also unable to determine net benefit due to heterogeneity[32-34]. The present study also examined the cost-effectiveness and preferences of GPs and older persons which, until now, has scarcely been investigated.

Strengths and limitations

The ISCOPE study was performed in a large number of practices in urbanized and sub-urbanized areas, involving single-handed practices and group practices, thereby guaranteeing generalizability to other practices in the Netherlands. Outcomes were measured during home visits, thereby increasing the reliability and completeness of the measurements. Because about 37% of the older people did not participate in the ISCOPE study, this could have led to a selection of healthier (or perhaps less healthy) older persons or people more likely to accept the suggested intervention. A non-response evaluation showed that non-participants were slightly more vulnerable than the participants; this difference might decrease with more extensive reminding procedures.

We were unable to obtain repeated assessments over a longer period. Repeated assessments might have amplified the proactive aspect of the intervention, possibly leading to a detectable effect on the outcomes.

Possible reasons for no effect in functioning

There are a few possible reasons for the lack of effect on the functioning of older persons in the present study. First, many changes in the care for older people in primary care have been instigated since the early 1990s[5]. The present study started in a climate of growing interest in preventive and proactive care for older people, which ensured enthusiasm

among participating GPs; government and care professionals were already moving in this direction. In 2007 the National Program for Elderly Care was set up, aiming to improve the quality of care for older people by developing coherent care better suited to the individual needs of older persons[35]. Although this climate of change implies that GPs were keen to participate in this study, no extra provisions (i.e. financial compensation to implement proactive care for older people) were yet in place; this keeps the risk of contamination in the usual care practices low. However, GPs (also in the control group) might have had an increased awareness of the need to work proactively for their older patients, as policy reports on this subject were issued in 2007 and 2010 (mission statements of the Dutch College of General Practice (DCGP)[36] and of the Royal Dutch Medical Association[37], and a guideline for the care for older people in general practice issued by the DCGP[38].

Second, unsolicited care programs or other devices might not work because those who would expect benefit from the offered service or device have already obtained it[38-40]. In this study, because the initiative for a care plan did not originate from the participant, executing the plan did not bring the desired changes.

Third, interventions targeted at specific risk factor management may be more effective than organizational interventions with a broader focus[32-33]. Indeed, the focus of our intervention may have been too broad and may have diluted the effect of each particular outcome measure, thus reducing the power to detect a difference. For this reason, we used quality of life as primary outcome and we also investigated combined scores of questionnaires as a secondary outcome; however, this also revealed no effect of the intervention.

Fourth, the intervention may not have been sufficiently intense to be able to cause effect. However, this explanation seems unlikely since one meta-analysis demonstrated that the intensity of the intervention made no difference to its effectiveness[5]. Possibly, the participants were relatively healthy with little room for improvement. However, a sensitivity analysis in the group with problems in 4 domains also failed to show an effect.

Five, a change in approach in organization and delivery of care does not necessarily lead to effects on the level of functioning or quality of life of the patient. The two meta-analyses showed no positive effect on functioning of any of the interventions, possibly due to the use of non-responsive ADL and IADL instruments[5,6]. Perhaps outcomes related to healthcare delivery, such as patient experience with continuity of care[41] , or more individualized outcomes such as goal attainment scaling[42], might have elicited more response than traditional outcome measures of functioning[43-46]. Unfortunately, at the start of the present study, these latter outcomes were not widely available for practical use in research with community-dwelling older people, but might be promising for use in future studies.

Six, a randomized trial may not be appropriate for this sort of interventions as the services offered comprise a complex mix of uncontrollable variables embedded in a social process, more than a treatment program alone[47]. The success of the offered services depends on factors other than functioning (such as building a relationship with the client, the perceived need for care, past experiences with health care, etc.) which cannot be measured or controlled in such a way as to meet the requirements of randomized controlled trials. The increase in satisfaction with care among both the older people and the GPs might reflect these factors. Although failure to show an effect should not be used solely as an excuse to discontinue the service, it remains important to find evidence regarding the cost-effectiveness of new ways of working.

Implications

The question remains as to which outcomes will convince healthcare professionals and policymakers in their decision-making regarding implementation of an intervention. The present study showed no beneficial effect on functioning and quality of life of older persons, or on healthcare costs; therefore, this integrated care model cannot be recommended for this particular goal. Nevertheless, in the Netherlands, healthcare organization for older people in general practice has assumed its own momentum. GPs are increasingly interested and motivated to implement proactive care to prevent functional decline in vulnerable older persons[48] and see this as an improvement of their care. Since 2011, health insurers in the Netherlands have provided funding to GPs to innovate services towards proactive care for older people, encompassing two main elements: case finding and care plans. This lack of congruence between research and policy is an issue that should receive more attention.

Integrative and proactive care for older community-dwelling people will probably be an essential instrument in primary care to be able to manage the care since (in the present political climate) the need to cut costs results in more older people living independently in the community rather than in care homes, but still requiring health care. This study also shows that GPs working with a proactive care plan report the benefit of increased stability in the care of older persons. We think that horizontal care using care plans for older people with complex problems can be a valuable tool in general practice. However, since no direct beneficial effect was found for older persons, based on this study we cannot recommend this intervention to improve patient outcomes in general practice.

REFERENCES

1. Fried LP, Storer DJ, King DE, Lodder F. Diagnosis of illness presentation in the elderly. J Am Geriatr Soc. 1991 Feb;39:117-23.
2. Tinetti ME. Performance-oriented assessment of mobility problems in elderly patients. J Am Geriatr Soc. 1986 Feb;34(2):119-26.
3. Fried TR, McGraw S, Agostini JV, Tinetti ME. Views of older persons with multiple morbidities on competing outcomes and clinical decision-making. J Am Geriatr Soc. 2008 Oct;56:1839-44.
4. De Maeseneer J, Boeckxstaens P. James Mackenzie Lecture 2011: Multimorbidity, goal-oriented care, and equity. Br J Gen Pract. 2012 Jul;62:e522-4.
5. Beswick AD, Rees K, Dieppe P, Ayis S, Gooberman-Hill R, et al. Complex interventions to improve physical function and maintain independent living in elderly people: a systematic review and meta-analysis. Lancet. 2008 Mar 1;371:725-35
6. Lin JS, Whitlock EP, Eckstrom E, Fu R, Perdue LA, et al. Challenges in synthesizing and interpreting the evidence from a systematic review of multifactorial interventions to prevent functional decline in older adults. J Am Geriatr Soc. 2012 Nov;60:2157-66
7. Boult C, Reider L, Frey K, Leff B, Boyd CM, et al. Early effects of „Guided Care" on the quality of health care for multimorbid older persons: a cluster-randomized controlled trial. J Gerontol A Biol Sci Med Sci. 2008 Mar;63:321-7.
8. Van Houwelingen AH, Den Elzen WPJ, Le Cessie S, Blom JW, Gussekloo J. Consequences of interaction of functional, somatic, mental and social problems in community-dwelling older people. PLoS One. 2015 Febr; Accepted for publication.
9. Junius-Walker U, Stolberg D, Steinke P, Theile G, Hummers-Pradier E, et al. Health and treatment priorities of older patients and their general practitioners: a cross-sectional study. Qual Prim Care. 2011;19:67-76.
10. Schellings R, Kessels AG, ter Riet G, Sturmans F, Widdershoven GA, et al. Indications and requirements for the use of prerandomization. J Clin Epidemiol. 2009 Apr;62:393-9.
11. Schellings R, Kessels AG, Ter Riet G, Kleijnen J, Leffers P, et al. Members of research ethics committees accepted a modification of the randomized consent design. J Clin Epidemiol. 2005 Jun;58:589-94
12. Smelt AF, van der Weele GM, Blom JW, Gussekloo J, Assendelft WJ. How usual is usual care in pragmatic intervention studies in primary care? An overview of recent trials. Br J Gen Pract. 2010 Jul;60:e305-18
13. Weeks SK, McGann PE, Michaels TK, Penninx BW. Comparing various short-form Geriatric Depression Scales leads to the GDS-5/15. J Nurs Scholarsh 2003;35:133-137.
14. Steverink S, Slaets JP, Schuurmans H, Van Lis M. Measuring frailty: developing and testing the GFI (Groningen frailty Indicator). Gerontologist 2001;41:236-237.
15. McCusker J, Bellavance F, Cardin S, Trepanier S. Screening for geriatric problems in the emergency department: reliability and validity. Identification of Seniors at Risk (ISAR) Steering Committee. Acad Emerg Med 1998;5:883-893.
16. de Jong Gierveld, J., & Kamphuis, F.H. The development of a Rasch-type loneliness-scale. Applied Psychological Measurement. 1985; 9:289-299
17. Stek ML, Gussekloo J, Beekman AT, van Tilburg W, Westendorp RG. Prevalence, correlates and recognition of depression in the oldest old: the Leiden 85-plus study. J Affect Disord. 2004 Mar;78:193-200

18. Artero S, Touchon J, Ritchie K. Disability and mild cognitive impairment: A longitudinal population-based study. Int J Geriatr Psychiatry 2001;16: 1092–1097.
19. Drewes YM, den Elzen WP, Mooijaart SP, de Craen AJ, Assendelft WJ, et al. The effect of cognitive impairment on the predictive value of multimorbidity for the increase in disability in the oldest old: the Leiden 85-plus Study. Age Ageing. 2011 May;40:352-7
20. Perissinotto CM, Stijacic Cenzer I, Covinsky KE. Loneliness in older persons a predictor of functional decline and death. Arch Intern Med. 2012 Jul 23;172:1078-83
21. Hertogh CMPM, Deerenberg-Kessler W, Ribbe MW. The problem-oriented multidisciplinary approach in Dutch nursing home care. Clin Rehabil. 1996; 10:135-142
22. Kempen GI, Miedema I, Ormel J, Molenaar W. The assessment of disability with the Groningen Activity Restriction Scale. Conceptual framework and psychometric properties. Soc Sci Med. 1996 Dec;43:1601-10.
23. Cantril H. (1965). The pattern of human concerns. New Brunswick, NJ: Rutgers University Press.
24. Lutomski JE, Baars MA, Schalk BW, Boter H, Buurman BM, et al; TOPICS-MDS Consortium. The development of the Older Persons and Informal Caregivers Survey Minimum DataSet (TOPICS-MDS): a large-scale data sharing initiative. PLoS One. 2013 Dec 4;8(12):e81673.
25. Collins K, O'Cathain A. The continuum of patient satisfaction—from satisfied to very satisfied. Soc Sci Med. 2003 Dec;57:2465-70.
26. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975 Nov;12:189-98
27. D'Ath P, Katona P, Mullan E, Evans S, Katona C. Screening, detection and management of depression in elderly primary care attenders. I: The acceptability and performance of the 15 item Geriatric Depression Scale (GDS15) and the development of short versions. Fam Pract. 1994 Sep;11:260-6
28. de Jong Gierveld, J., & Kamphuis, F.H. The development of a Rasch-type loneliness-scale. Applied Psychological Measurement 1985;9: 289-299.
29. de Ruijter W, Westendorp RG, Macfarlane PW, Jukema JW, Assendelft WJ, et al. The routine electrocardiogram for cardiovascular risk stratification in old age: the Leiden 85-plus study. J Am Geriatr Soc. 2007 Jun;55:872-7.
30. Killip S, Mahfoud Z, Pearce K. What is an intracluster correlation coefficient? Crucial concepts for primary care researchers. Ann Fam Med 2004 May;2:204-8
31. Metzelthin SF, van Rossum E, de Witte LP, Ambergen AW, Hobma SO, et al. Effectiveness of interdisciplinary primary care approach to reduce disability in community dwelling frail older people: cluster randomised controlled trial. BMJ. 2013 Sep 10;347:f5264.
32. de Bruin SR, Versnel N, Lemmens LC, Molema CC, Schellevis FG, et al. Comprehensive care programs for patients with multiple chronic conditions: a systematic literature review. Health Policy. 2012 Oct;107:108-45.
33. Smith SM, Soubhi H, Fortin M, Hudon C, O'Dowd T. Managing patients with multimorbidity: systematic review of interventions in primary care and community settings. BMJ. 2012 Sep 3;345:e5205.
34. Smith SM, Soubhi H, Fortin M, Hudon C, O'Dowd T. Interventions for improving outcomes in patients with multimorbidity in primary care and community settings. Cochrane Database Syst Rev. 2012 Apr 18;4:CD006560.
35. http://www.nationaalprogrammaouderenzorg.nl/english/the-national-care-for-the-elderly-programme/
36. http://nhg.artsennet.nl/English.htm
37. http://knmg.artsennet.nl/Over-KNMG/About-KNMG.htm

38. de Craen AJ, Gussekloo J, Blauw GJ, Willems CG, Westendorp RG. Randomised controlled trial of unsolicited occupational therapy in community-dwelling elderly people: the LOTIS trial. PLoS Clin Trials. 2006 May;1:e2.
39. van der Weele GM, de Waal MW, van den Hout WB, de Craen AJ, Spinhoven P, et al. Effects of a stepped-care intervention programme among older subjects who screened positive for depressive symptoms in general practice: the PROMODE randomised controlled trial. Age Ageing. 2012 Jul;41:482-8.
40. Gussekloo J, de Bont LE, von Faber M, Eekhof JA, de Laat JA, et al. Auditory rehabilitation of older people from the general population-the Leiden 85-plus study. Br J Gen Pract. 2003 Jul;53:536-40
41. Uijen AA, Schellevis FG, van den Bosch WJ, Mokkink HG, van Weel C, et al. Nijmegen Continuity Questionnaire: development and testing of a questionnaire that measures continuity of care. J Clin Epidemiol. 2011 Dec;64:1391-9
42. Rockwood K, Stolee P, Fox RA. Use of goal attainment scaling in measuring clinically important change in the frail elderly. J Clin Epidemiol. 1993 Oct;46:1113-8
43. Steenbeek D, Gorter JW, Ketelaar M, Galama K, Lindeman E. Responsiveness of Goal Attainment Scaling in comparison to two standardized measures in outcome evaluation of children with cerebral palsy. Clin Rehabil. 2011 Dec;25:1128-39.
44. Rockwood K, Howlett S, Stadnyk K, Carver D, Powell C, et al. Responsiveness of goal attainment scaling in a randomized controlled trial of comprehensive geriatric assessment. J Clin Epidemiol. 2003 Aug;56:736-43
45. Rockwood K, Fay S, Song X, MacKnight C, Gorman M; Video-Imaging Synthesis of Treating Alzheimer's Disease (VISTA) Investigators. Attainment of treatment goals by people with Alzheimer's disease receiving galantamine: a randomized controlled trial. CMAJ. 2006 Apr 11;174:1099-105.
46. Wright JG, Young NL. The patient-specific index: asking patients what they want. J Bone Joint Surg Am. 1997 Jul;79:974-83.
47. Clark J. Preventive home visits to elderly people. Their effectiveness cannot be judged by randomised controlled trials. BMJ. 2001 Sep 29;323:708.
48. Drewes YM, Koenen JM, de Ruijter W, van Dijk-van Dijk DJ, van der Weele GM, et al. GPs' perspectives on preventive care for older people: a focus group study. Br J Gen Pract. 2012 Nov;62:e765-72.

Additional table 1. Baseline characteristics of participants with complex problems compared to participants without complex problems.[†]

	Complex problems n=1516	No complex problems n=1197	p-value
Age in years*	83.0 (79.5;87.4)	80.9 (77.9;85.1)	<0.001
Sex (% female)	1086 (71.6)	768 (64.2)	<0.001
>4 medications (%)	1172 (77.3)	645 (53.9)	<0.001
Cantril's ladder*	7 (6;8)	8 (7;8)	<0.001
GARS total score*	37 (29;46)	26 (21;33)	<0.001
BADL subscale score*	11 (9;15)	9 (9;10)	<0.001
IADL subscale score*	26 (19;32)	17 (12;23)	<0.001
MMSE score*	27 (25;29)	28 (27;29)	<0.001
GDS score*	3 (1;5)	1 (0;2)	<0.001
DJG score*	3 (1;6)	1 (0;3)	<0.001

*(median, IQR)

GARS	Groningen Activity Restriction Scale
BADL	Basic Activities of Daily Living
IADL	Instrumental Activities of Daily Living
MMSE	Mini Mental State Examination
GDS	Geriatric Depression scale
DJG	De Jong-Gierveld Loneliness scale

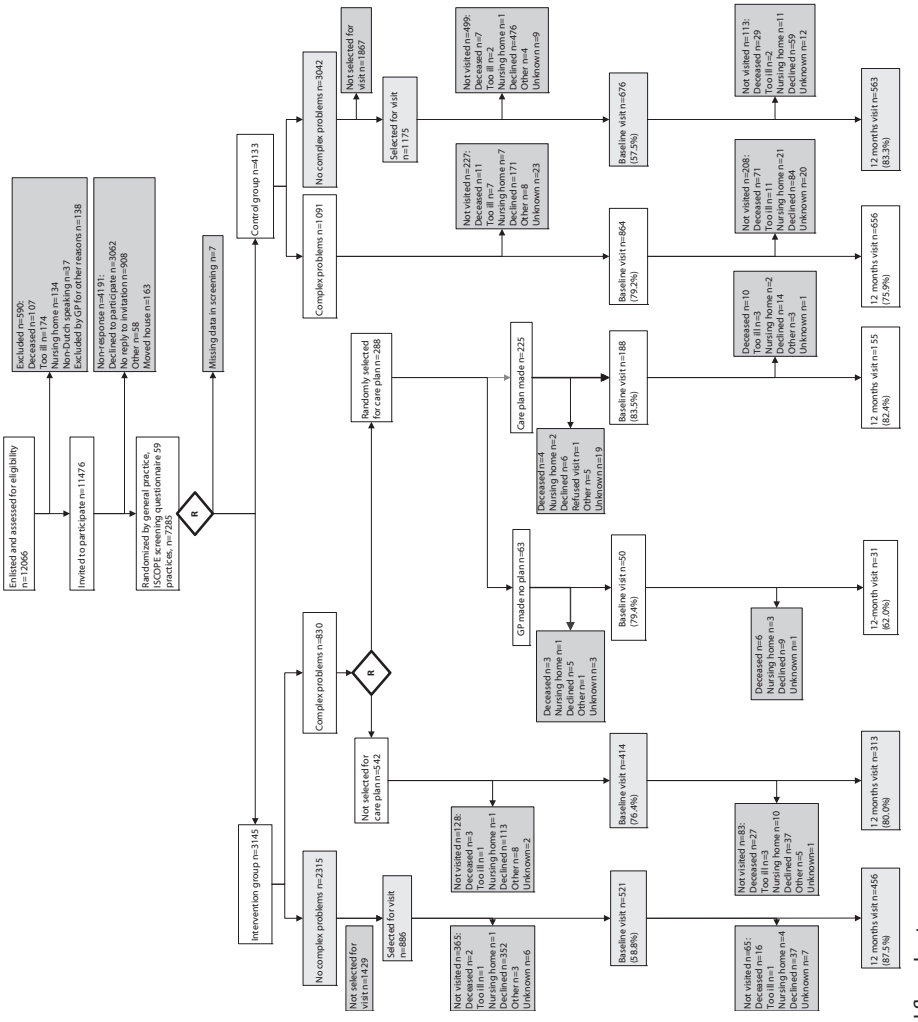
[†]Baseline and follow up measurements were performed for all participants with complex problems, for 60% randomly selected participants with scores on 0 or 1 domain and for 15% randomly selected participants with problems on 2 domains (see total flowchart).

Additional table 2. P values for difference in sex and reasons for non-participation between non-participants in intervention and control group with complex problems

Reason for non-participation	**p-value**
First visit	
Death	0.871
Too ill	0.646
Admission to nursing home	0.830
Declined	0.607
Second visit	
Death	0.153
Too ill	0.465
Admission to nursing home	0.830
Declined	0.607
Sex	
First visit	0.137
Second visit	0.871

Additional table 3. Outcomes informal caregivers in intention to treat analysis.

Outcome	Change in 1-year follow-up for informal caregivers in control group (n=143)	p-value	Extra change in informal caregivers in intervention group compared to control group (n=40)	p-value
Hours per week spent on care				
Household activities	0 (-0.1; 0.1)	0.474	-0.1 (-0.2; 0.1)	0.444
Personal care	0 (-0.1; 0.1)	0.674	0 (-0.2; 0.2)	0.970
Outdoor activities	0 (0; 0)	0.827	0 (0; 0.1)	0.403
Burden of care (0-10)	0.5 (0.1;0.8)	0.024	-0.4 (-1.2;0.4)	0.323
Feeling of happiness (0-10)	-2.0 (-2.5;-1.4)	<0.001	0 (-1.1;1.2)	0.933



Additional figure 1. Total flowchart.



9

GENERAL DISCUSSION

The results of the work presented in this thesis shed new light on two important issues for evidence-based general practice care for older people:

1. Feasibility of (proactive) identification of older people with complex problems.
2. Effectiveness of proactive integrated care for older people with complex problems in general practice.

This chapter discusses the implications for theory and general practice and makes some recommendations for future research. The main results regarding the major aims of this thesis are discussed separately below.

FEASIBILITY OF PROACTIVE IDENTIFICATION OF OLDER PEOPLE WITH COMPLEX PROBLEMS

Older people at risk of a decline in functioning should be proactively identified in order to provide targeted integrated interventions. Functional decline will eventually lead to disability and dependency upon (informal) caregivers and, for most older people, this is an undesired outcome. Problems on four domains of health (functional, somatic, mental and social; Figure 1) are individually or in combination associated with an increased risk of functional decline. Older people with complex problems (i.e. 'multiple problems in multiple domains of health that often interact', Figure 1'[1]), might be at even higher risk of functional decline. Therefore, these older persons will probably benefit most from interventions directed to the prevention or postponement of functional decline.

In a prospective study of the oldest old (aged 85 years at baseline) in the general population we used a multistate survival model to investigate the course of disability, functional decline and death, as well as their predictors, during 5 years of follow-up (*Chapter 2)*. In contrast to a conventional Coxproportional hazard model (which allows only one transition: between an 'alive' state to a 'death' state), this survival model allows the movement of study participants between various states of disability. Results of this study show that disability is a dynamic process in the oldest old. Even though most transitions were directed to more functional impairment, some transitions were directed to improvement. Therefore, a multi-state model may be a better method to study the course of disability in a prospective survival study than a model that assumes that older people only decline in functional status.

In addition, we found that prior disability, chronic disease, depressive symptoms and cognitive impairment were individually associated with functional decline. Interestingly, these health problems are components of three of the four domains of complex problems: functional problems (disability), somatic problems (chronic disease) and

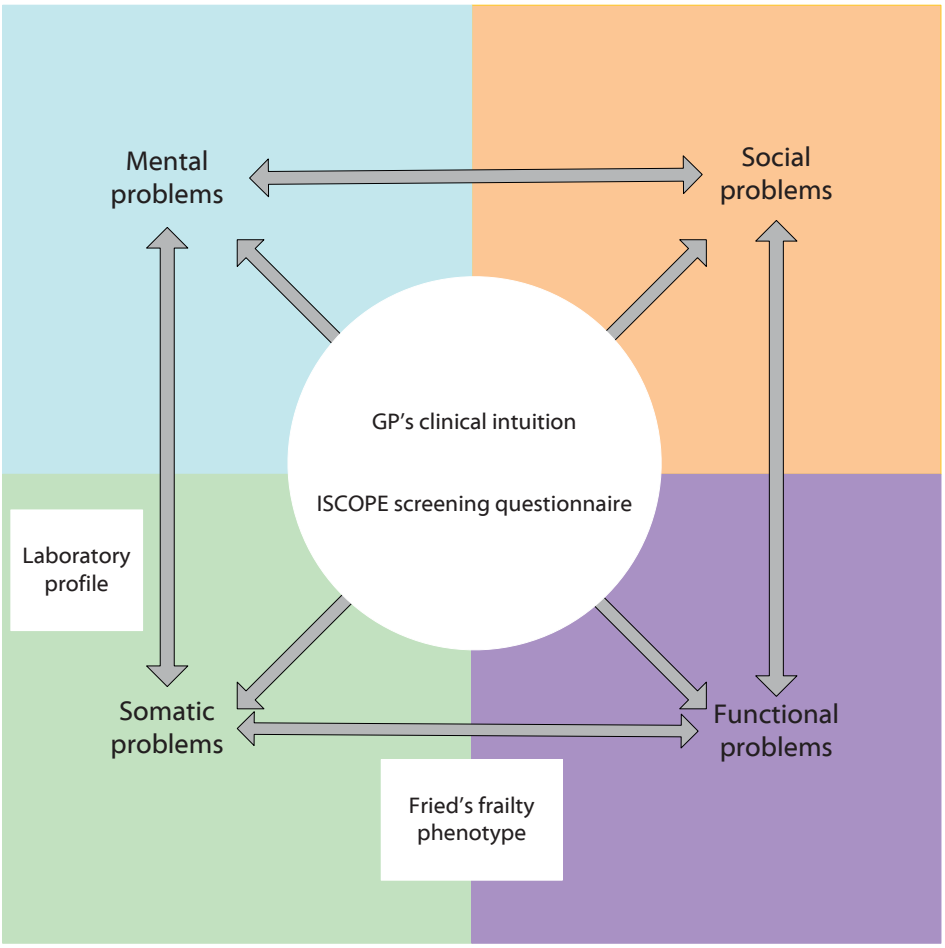


Figure 1. Conceptual model of complex problems in older people.

mental problems (depressive symptoms and cognitive impairment). Therefore, these results imply that those three domains are predictive for functional decline. In addition, evidence for an association between the social domain and functional decline merged from previous research, i.e. an analysis in the Leiden 85-plus Study showed that loneliness, a component of the social domain, is associated with mortality[2]. These results were confirmed in the Health and Retirement study, which also found an association between loneliness and functional decline[3]. Another study among the fittest community-dwelling older adults in Canada showed that the concept of 'social vulnerability', which is also a component of the social domain and includes social support, living situation, social engagement, socio-economic status etc., is associated with mortality[4]. The results of these three studies indicate that the social domain is associated with functional decline and mortality.

In the ISCOPE study, we showed that the combination of problems on the functional, somatic, mental and social domain was associated with disability, cognitive impairment, depressive symptoms, feelings of loneliness, poor health-related quality of life, and more GP contact time *(Chapter 4*). Results indicate not only a negative trend across the number of affected domains, but also a negative interactive effect for older persons with problems on all four domains. These results demonstrate that interaction of the four domains, with an accumulating effect on poor health, can be demonstrated when older persons have problems on four domains. Thus, older people with complex problems are at risk of poor health outcomes, including disability.

COMPARISON OF MEASURES TO IDENTIFY COMPLEX PROBLEMS

Health indicators for comparison of identification measures

Since older people with complex problems often have poor health, the indicators of poor health can be used to evaluate measures to identify complex problems (Table 1). In this thesis, we evaluated the accuracy and effectiveness of identification measures to identify poor health outcomes. Most of these health indicators also included components of the domains that determine complex problems. However, the health indicators used in this thesis (Table 1) were assessed using validated questionnaires, whereas the domains are usually assessed with short (and often not fully comprehensive) identification measures. We made this choice for practical reasons, because validated questionnaires for the domains are extensive and therefore not feasible to be used as an identification measure.

Each of the four health domains can be used individually or in combination as identification measures for complex problems. Each health domain is assumed to have a corresponding (poor) health indicator measured by an extensive validated questionnaire.

Table 1. Poor health indicators applied in this thesis

Cross-sectional	Prospective
	Change in
Disability	Disability
Life satisfaction/quality of life	Life satisfaction/quality of life
Depressive symptoms	Depressive symptoms
Loneliness	Loneliness
Poor cognitive function	Poor cognitive function
Use of GP care	Use of GP care
Chronic disease	Mortality
	Hosptalization

In this thesis, the corresponding health indicators were disability and functional decline for the functional domain, chronic disease and mortality for the somatic domain, cognitive impairment for the mental domain, and loneliness for the social domain. Quality of life and healthcare use were health indicators that were considered to correspond with all these domains. The results of *Chapters 4 and 5* confirm that four briefly assessed health domains are indeed associated with their corresponding health indicators (as an outcome).

The yield on health indicators of identification measures

In this thesis, we examined five measures to identify older people with complex problems: a profile of laboratory parameters, reduced handgrip- and quadriceps muscle strength, the Fried frailty phenotype criteria, the clinical intuition of the GP and, the ISCOPE screening questionnaire. The main results relating to these measures are briefly discussed below.

The profile of laboratory parameters (*Chapter 3*) was associated with 5-year mortality in the general population of older people, aged 85 years at baseline. The predictive accuracy of this profile was similar to that of two other known predictors (disability in instrumental activities of daily living [IADL] and slow gait speed). Based on these results, this profile might be an appropriate measure to identify complex problems; however, it is unknown whether this somatic laboratory profile is also predictive for health indicators other than mortality. Theoretically, this profile could be a good predictor for functional decline, because most of the components have been individually associated with poor functional status[5, 6], and to diseases related to poor functional status, such as stroke[7] or functional decline[8-11].

Muscle strength is used often as a surrogate measure for sarcopenia[12], which is the degenerative loss of skeletal muscle. Sarcopenia is thought to be causally related to functional decline[13, 14]. We found that both handgrip- and quadriceps muscle strength were independently associated with poor health indicators at baseline *(Chapter 7)*. In contrast to hand grip strength, which was prospectively associated with disability in BADL (functional decline) and quality of life, quadriceps muscle strength had no prospective association with poor health indicators. These results indicate that both measurements of muscle strength could be used as a measure for complex problems. However, handgrip strength and quadriceps strength were only moderately correlated, which suggests that these two muscle parameters might represent different properties at old age. Since handgrip strength was the only measure that was associated with prospective poor health indicators, and this measurement is easier to obtain than quadriceps strength, handgrip strength would be recommended for general practice. As reduction in both

muscle parameters was associated with the poorest health indicators, this combination could be used to identify the most complex subpopulation of older people.

We compared the Fried frailty phenotype[15] criteria and the clinical intuition of the GP with the ISCOPE screening questionnaire with regard to their yield on poor health indicators. The ISCOPE screening questionnaire is a new measure that was introduced in the context of the Integrated Systematic Care for Older PEople study *(Chapter 8*) and was developed based on the statement of the DCGP *(Chapter 5)*. The questionnaire briefly assesses the four domains (4-7 items per domain) involved in complex problems (Figure 1). We found that the group of older people classified as having complex problems only moderately overlapped for these three measures (*Chapter 6)*. The proportion of the population of older people classified as having complex problems also differed for each measure. Moreover, the three measures had a different yield on health indicators.

In addition, we found that the Fried frailty phenotype had a very strong association with disability and with the number of chronic diseases. In contrast, the ISCOPE screening questionnaire was associated with health indicators of all domains and had a strong association with loneliness compared to the other measures. Compared to the Fried frailty phenotype and the ISCOPE screening questionnaire, the GP's clinical intuition had a strong association only with GP contact time.

In conclusion, since all five measures classified different groups of older people as having complex problems, and the association with health indicators also differed, one can conclude that these five measures may represent different operationalizations of the concept 'complex problems'.

Gold standard for complex problems?

At the start of the research described in this thesis, no gold standard for complex problems was available. This led to difficulties when comparing the five measures, i.e. the individual measures could not be tested against a gold standard test to evaluate which was the best measure for complex problems. Moreover, because all measures had a different yield on health indicators and overlapped only moderately, none of the five measures is a candidate for a gold standard test.

The question then arises whether it is in fact possible to find a gold standard for complex problems. A gold standard test should be the most accurate test for a condition. According to this definition, the concept of 'complex problems' would be the condition to identify. A gold standard test should identify older people with complex problems as having complex problems, and older people without complex problems as having no complex problems, with low numbers of false-negative or false-positive results (high

sensitivity and specificity). Since 'complex problems' is a very broad concept, finding a uniform gold standard will be very difficult.

Suitable identification measure for general practice

Despite the lack of a gold standard and the different operationalizations of the concept of complex problems, all of the studied measures identify older people with poor health outcomes. Therefore, these measures can be used to identify these older people in general practice. However, none of the measures can be recommended as the most suitable for general practice. When selecting a measure, a GP may take into account:

1. The intended intervention
   If a GP plans to target complex older people with loneliness, the ISCOPE screening questionnaire might be the measure of choice, since this measure was the most strongly associated with loneliness (*Chapter 6*). When a GP plans to identify a subpopulation of complex older people with disability, the Fried frailty phenotype *(Chapter* 6) or the measurement of muscle strength *(Chapter 7)* might be the best measure. If a GP aims to assess mortality risk, a profile of laboratory parameters could be used to exclude older people with poor life expectancy from, for example, extensive screening programs. Because the laboratory profile provides information beyond age alone, it can provide the GP with valuable information *(Chapter 3*).
2. The workload involved with each measure
   The clinical intuition of the GP is readily available for every GP and is not time consuming. In contrast, administration of the Fried frailty phenotype and the measurement of muscle strength is difficult, because these performance tests require training and are time consuming. The ISCOPE screening questionnaire can be sent by post and is therefore easy to apply in general practice. Although laboratory parameters are generally loaded directly in the GPs' electronic patient record, measuring the laboratory parameters of all older people can be a costly process for a GP practice. Therefore, the clinical intuition of the GP, the ISCOPE screening questionnaire and the profile of laboratory parameters, could be applied in general practice.
3. The intention for a systematic inventory of the older population
   If GPs aim for a systematic inventory of the presence of complex problems in older patients in their practice, the ISCOPE screening questionnaire might be appropriate, because the total population of people aged 75 years and over can be easily approached via this postal questionnaire (on average 150 persons per practice). The Fried frailty phenotype and the measurement of muscle strength is not suitable for systematic inventories because of the above-mentioned workload. Therefore, the Fried frailty phenotype might be used as a second step when older persons are considered by the GP to have complex problems. The laboratory profile is also not

suitable for systematic inventories, because it is a very costly procedure to obtain blood samples from all older people in a general practice.

Appropriateness of screening for complex problems

In the ISCOPE study, we used systematic screening to identify complex problems. All people aged 75 years and over (apart from a small group of very ill people who were excluded by their GP) received a postal invitation to participate in the ISCOPE study. The response rate of the ISCOPE study was moderate but, presumably, the response rate will be higher when older persons are screened by their GP, because informed consent to join a comprehensive trial is then not necessary. Therefore, systematic screening for complex problems might be an appropriate method to select complex older persons for a targeted integrated intervention in general practice. However, such population screening programs have to fulfil the 10 criteria of screening programs for disease, as published by Wilson and Jungner[16]:

1. The first criterion is that the condition sought, should be an important health problem. This criterion applies to complex problems, which has a high prevalence and has important consequences for the health of older people. Complex problems are associated with disability, depressive symptoms, cognitive function, feelings of loneliness and health-related quality of life (*Chapter 4* and *Chapter 6*). Moreover, complex problems also have consequences for healthcare use, since older people with problems on four domains have more contact with their GP at baseline, but also during 12-months of follow-up; this implies that complex problems are also a predictor for future GP care use. Therefore, the first Wilson and Jungner criterion can be fulfilled.
2. The second criterion is that there should be an accepted treatment for patients with recognized disease. Although studies have demonstrated a small but significant effect of integrated care for older people[17, 18], in this thesis, an integrated care-action plan did not have an effect on older people with complex problems in general practice *(Chapter 8*). Therefore, the second criterion of Wilson and Jungner is not yet fulfilled.
3. The availability of facilities for diagnosis and treatment is the third criterion. Although 'diagnosing' complex problems could relatively easily be facilitated with one of the above-mentioned measures (with the postal ISCOPE screening questionnaire, the population can easily be reached), there are no facilities for treatment because an effective treatment is not available (criterion 2). Therefore, the third criterion cannot be fulfilled. Further research is needed to find an effective treatment and, when this treatment is found, facilities can be established.
4. There should be a recognizable latent state or an early symptomatic state of the disease. Since older people with complex problems are at risk for functional decline

and the aim of screening for complex problems would be to postpone functional decline, complex problems can be considered to be an early symptomatic state. This criterion can therefore be fulfilled.

5. The fifth criterion is a suitable test or examination. This thesis is devoted to a search for a suitable test. This search yielded inconclusive results, since none of the five studied measures could be recommended as the most suitable test. Therefore, the fifth criterion cannot be fulfilled.
6. The sixth criterion is an acceptable test. Although we did not actually ask the older participants, it can be assumed that screening with a postal questionnaire would be acceptable, whereas screening with laboratory tests or performance tests might entail some resistance. Therefore, with the ISCOPE screening questionnaire we have an acceptable test which fulfils the sixth criterion.
7. To fulfil the seventh criterion, the natural history of the condition, including development from latent to declared disease, should be adequately understood. This is not the case for complex problems. Since 'complex problems' is a concept with various operationalizations it needs further unravelling. Moreover, it is unknown how older people become 'complex' and whether or not having complex problems is a dynamic process, with transitions in and out of complex problems. Therefore this criterion has not yet been met.
8. There should be an agreed policy on whom to treat as patients. Since the five studied measures all classify different groups of older people as complex, it would be very difficult to fulfil this criterion.
9. The ninth criterion includes the costs of screening, which should be economically balanced in relation to possible expenditure on medical care as a whole. The ISCOPE study, which included screening for complex problems and subsequently an integrated care-action plan for older people with complex problems, was not cost-effective. Therefore, this ninth criterion is not fulfilled.
10. The tenth criterion is that screening should be a continuing process and not a one and for all project. When a screening program for complex problems is started, it is intended as a continuing process. However, it is unknown what the frequency of screening should be. Further research needs to establish an appropriate frequency for this screening. Therefore, this criterion is not yet fulfilled.

In conclusion, population screening for complex problems fulfils three of the Wilson and Jungner criteria (criterion 1, 3 and 6). It is uncertain whether two criteria are or can be fulfilled (criterion 4 and 10), and five criteria are not (yet) fulfilled (criterion 2,5, 7, 8 and 9). Therefore, systematic population screening for complex problems is not yet appropriate. Most of the criteria need more research, i.e. to find an (cost-) effective treatment for complex problems (criterion 2, 3 and 9),on the natural history of complex problems

(criterion 7), and to establish an adequate frequency of screening (criterion 10). If these criteria can be substantiated, population screening will deserve consideration again.

Case finding

Since systematic population screening for complex problems is not appropriate, another method is needed to identify older people with complex problems in general practice. Case finding involves screening a smaller group of people based on the presence of known risk factors. This might be an appropriate method to identify older people with complex problems. The results of this thesis indicate several possibilities to apply this method:

1. Alertness for non-responders
   In the ISCOPE study, older people who did not respond were more often appraised to be vulnerable by their GP, and were often visited at home by their GP. These results might imply that older people who do not respond are in fact more complex than older people who respond. Possibly, older people who tend not to respond to preventive treatment in general practice (e.g. influenza vaccination) might be more interesting candidates for interventions directed to complex problems, because the above-mentioned results indicate that they might be more complex than older people who do respond. GPs could use this information to increase their alertness for older people who tend to be non-responders.
2. Use of GP's clinical intuition
   The results of *Chapter 6* show that older people with poor health indicators could be identified by the clinical intuition of the GP. Compared to the ISCOPE screening questionnaire and the Fried frailty phenotype, the intuition of the GP had a strong association with GP contact time, which could indicate that the GP's intuition is not only a measure for complex problems in itself, but also for care complexity, which is related to difficulties in the care delivery process[19] *(Chapter 6)*.GPs could use this intuition to find older people with care complexity in their practice. If their intuition assesses an older person to be complex, this older person will need more GP care in the future. GPs could use this information to identify older persons for interventions to lower the care needs of these older persons.
3. Laboratory monitoring in older people
   Most older people are regularly monitored with laboratory parameters because they suffer from chronic diseases, including diabetes mellitus, hypertension and cardiovascular diseases. This regular monitoring could be extended with additional parameters, resulting in a complete laboratory profile on a regular basis. The results of the laboratory monitoring could be used to identify cases of older persons that are at high risk of mortality.

A disadvantage of case finding is that it is impossible to identify all older persons with complex problems, because only individuals with known risk factors (e.g. non-responders, GPs clinical intuition, older people who are regularly monitored with laboratory parameters) are identified. People without known risk factors will be missed by these methods. However, if these three methods are combined, they may allow to obtain a reasonably complete overview of the older persons with complex problems within a GP practice.

EFFECTIVENESS OF PROACTIVE INTEGRATED CARE FOR OLDER PEOPLE IN GENERAL PRACTICE

Proactive integrated care was suggested as a solution for uncoordinated care in older people with complex problems[1, 20]. In the ISCOPE study, a proactive integrated care plan had no direct effect on functional decline or quality of life for older people with complex problems *(Chapter 8)*.There are two possible explanations for this lack of effect: 1) there is indeed no direct effect of proactive integrated care, or 2) there is an effect (direct or not), but we have failed to demonstrate this effect within the ISCOPE study.

There is a possibility that proactive integrated care might have no direct effect on older persons in itself, because it is theoretically simply not a suitable way to deal with complex problems. However, because some studies demonstrated small but significant effects[17, 18] this explanation seems implausible. Moreover, integrated care has become standard for some diseases and in some general practices. Our study shows that GPs preferred proactive integrated care, and older people were slightly more satisfied in the intervention group than in the usual care group *(Chapter 8)*.Therefore, we may assume that there is an effect of integrated care, but that we could not demonstrate this effect. Several methodological issues might need to be addressed before we can draw definite conclusions about these items.

Methodological considerations for future studies

Target group

In the ISCOPE study, the target group for the integrated care plan were older people who screened positive for complex problems. In a previous review, it was suggested that interventions directed to the prevention of disability may be more effective in low-risk persons[21]. Persons that were selected for our intervention might have been too complex. This was confirmed by the results of focus group interviews of eight GPs in the intervention group. They indicated that the older people selected for the intervention

were not always the most appropriate people. Some older people seemed to use the screening to get more attention, or had problems that had been extensively dealt with before. Others indicated problems that could not be altered.

An intervention directed at persons that might have problems on only one or two domains could be more effective in preventing these older persons to develop problems on all of the domains. Such an intervention might prevent further deterioration into complex problems.

Avoid behavioural change of care professionals in usual care group

The GPs in the intervention group were compared to a group of GPs that was assumed to provide usual care. However, before randomization, most participating GPs were enthusiastic about integrated care and hoped to be randomized in the intervention group. It is known from previous research that (undesired) behavioural change of participating care professionals is often present in a usual care control group[22]. Hence, it is questionable whether GPs in the control group did or did not change their behaviour.

Behavioural change among the GPs in the control group is all the more likely since a statement of the Dutch college of General Practitioners (DCGP) was published before the start of the ISCOPE study and recommended integrated care for older people (in 2007)[1]. This statement was available for all GPs. During the study, much attention in the Netherlands was focused on optimization of medical care for older persons. In 2009, the Dutch Royal Medical Association published a policy report on care for older people[23]. Moreover, the theme of the yearly conference of the DCGP in 2009 was 'Care for older people in general practice'. This conference encouraged GPs to approach their older patients proactively and provide integrated care. All GPs could attend this conference, including GPs from the usual care group. This societal attention for older people with complex problems might have stimulated a behavioural change in GPs who were assumed to provide usual care. This behavioural change might have diluted the effect of an integrated care action plan for older people with complex problems in the intervention group. Future research on integrated care interventions should aim to prevent this 'contamination' of the usual care group, but this is also very difficult. A study with a cluster randomized stepped-wedge design might help to avoid this contamination. In such a design every cluster eventually receives the intervention[24]. This may prevent practices from starting the intervention during the time spent in the control phase.

Increase sample size

Primary care in the Netherlands has a very high standard. This might have made it very difficult to demonstrate an effect of an integrated care intervention, since there is little room for improvement. A larger sample size is probably needed to demonstrate a (probably small) effect of integrated care. In the context of the National Program of Elderly

Care (NPEC), a governmental program aiming to improve the quality of care for older people, ten studies of integrated care in general practice were set up. All these studies used the same minimal dataset, which included measures on functional status and quality of life, as an outcome[25]. Therefore the results of these studies could be combined in an individual patient data (IPD) meta-analysis to see whether there is an overall effect of integrated care in general practice on functional outcomes and quality of life in older people.

Development of evaluation tools for integrated care interventions

Maintaining their functional status and quality of life is important to older people[26]. Therefore, the aim of the ISCOPE study was to prevent functional decline and/or decrease in quality of life. However, two recent reviews showed that complex interventions to prevent functional decline had no (or no clinically relevant) effect[17, 18]. Therefore, to evaluate such complex organizational interventions measuring functional status or quality of life on the patient level may not be appropriate.

Goal attainment scaling is a way to evaluate whether patient goals are achieved[27] and is responsive to clinical changes[28]. A characteristic of an integrated care-action plan is that care goals are defined with the patient. Evaluating if these goals are achieved could be a better method to evaluate such an intervention. Therefore, goal attainment scaling could be a useful evaluation tool for further research on integrated interventions in primary care.

Funding for integrated care

GPs in the intervention group did not receive financial support to implement proactive integrated care in their practices. There was no funding for interdisciplinary consultation meetings; however, these are essential to collaborate with a multidisciplinary team. For the success of future integrated care interventions, funding for these meetings should be available. However, extra funding will not lead to a success of integrated care by itself, but should be combined with the suggestions above.

Considerations for future interventions in older people

The lack of effectiveness of the ISCOPE study might also be attributed to our intervention, for the following reasons.

Unmet care needs

In the ISCOPE study, unmet needs were not specifically considered in the integrated care-action plan. Unmet needs are defined as a (health) problem of an older person, that may be hidden or not immediately obvious to their physician. Moreover, this health problem has not been adequately addressed either by older persons themselves, their

family and friends, or their caregivers[29]. In a previous study, vision, hearing, mobility, falls, incontinence, depression and anxiety were identified as covering 69% of the most common unmet needs in older people[29]. Some of these problems can probably be dealt with using a relatively easy intervention. Therefore, it is important to consider unmet needs when designing an integrated care intervention. Addressing unmet needs by applying relatively small interventions might substantially improve the quality of life and/or functional status of older people. Therefore, when designing future interventions for older people with complex problems, unmet care needs should be considered and identified. The ISCOPE screening questionnaire, used to identify older people with complex problems in the ISCOPE study, included an open question that assesses which problems most hinder an older person. Although the results of this question were not taken into account in this thesis, the responses to this question might reflect the unmet needs of older people. The answers to this question may be used to identify unmet needs and to act upon these unmet needs.

An integrated intervention on population level

For optimal integrated care for older people, collaboration with other caregivers is essential. For individual GPs, it is difficult to set up a network of all caregivers and healthcare workers involved in the care for older people. Therefore, plans on an aggregation level higher than on the individual general practice level are needed. For example, within a village or city district all key players involved with elderly care could constitute a work group with representatives from all these key players. This workgroup connects the key players and could facilitate collaboration within a city district or village. This may facilitate integrated care for older people based on better collaboration between the healthcare professionals involved with an older person.

Collaboration with elderly care physician and GP with expertise in geriatrics

GPs might not have optimal competencies to carry out an integrated care intervention. In the Netherlands, one of the strengths of GPs is that they have generally known their patients for a relatively long time. This means they see the patient in the context of the longitudinal (medical) history, which can be considered as a vertical view on the problems and care for older patients. In the Netherlands, elderly care physicians receive a three-year training in the provision of care to very complex older people in nursing homes in collaboration with other caregivers, and are involved with these patients on a daily basis. Therefore, elderly care physicians have a broader (so-called horizontal) view on care for complex older people than GPs. Since recent years, elderly care physicians are increasingly involved with complex older people in primary care. These elderly care physicians advise GPs on integrated care interventions. Many initiatives to further

establish these collaborations are being developed[30] to the satisfaction of GPs, elderly care physicians and older patients.

In addition, since 2007, an increasing number of GPs have acquired expertise in geriatrics by following a 2-year postgraduate education program (core training) in geriatrics. These GPs have learned to adapt their practices towards the needs of an aging society and can also help other GPs to set-up integrated care in their practices

Whether collaboration with an elderly care physician or a GP with expertise in geriatrics resulted in positive effects on functional status and quality of life in the ISCOPE study, remains to be examined. However, collaboration with physicians that have expertise in geriatrics could help the GP to better organize elderly care in his practice; this is needed by most GPs because of the ageing population.

FUTURE

Recommendations for further research

Recommendations for research on identification of complex problems in older people

- When investigating measures to identify older persons at risk for functional decline in a prospective study, the fact that disability is a dynamic process should be taken into account. Therefore, multistate modelling should be used.
- The laboratory profile is a good measure to identify complex older persons at risk for mortality, but the predictive validity for functional decline is still unknown.
- Because of the various operationalizations of complex problems, this concept needs further unravelling, including the natural history and the interactive effect of the four domains determining complexity.
- Because systematic screening of the older population on complex problems does not fulfil the criteria of Wilson and Jungner, further research could investigate case-finding as a method to identify older persons with complex problems.

Recommendations for research on proactive integrated care

For future research on integrated care interventions in general practice, we need to consider the target group for integrated interventions. Interventions could be targeted at persons that are not complex, but might be at risk to become complex. Therefore, measures should be developed to identify this group, or existing measures adjusted to select this target group. In addition, an IPD meta-analysis of all studies in the NPEC will indicate if there is an effect of proactive integrated care in general practice. Moreover,

goal attainment scaling should be investigated as an evaluation tool for integrated interventions in general practice.

Implications for general practice

We have introduced five methods to identify a group of older persons with complex problems at risk of poor health. Not all of these measures covered all the domains that were associated with complex problems, but it became clear that complex older persons can be identified. GPs could use all five measures in their practices, but which measure to use should depend on the intended intervention, the workload involved with each measure, and the intention to systematically map their older population.

Screening for complex problems followed by an integrated care plan for older people who screened positive for complex problems cannot be recommended, because this integrated care model had no beneficial effect on functioning and quality of life, or on healthcare costs. Nevertheless, integrated care seems to have gained its own momentum. Several general practices in the Netherlands have implemented integrated care for older people. Although an integrated care plan has not yet been proven to improve patient outcomes in general practice, it might be a valuable tool for general practice when implementing integrated care.

CONCLUSION

The main conclusions of this thesis are that; 1) the item 'complex problems' has various operationalizations, all of which can be identified by relatively simple measures, and that 2) direct benefit from proactive integrated care for older people with complex problems could not be demonstrated, which might be attributed to the study design and/or to the intervention itself. Therefore, more studies are required and additional interventions need to be developed in order to improve the care for older persons in general practice.

REFERENCES

1. NHG-standpunt Toekomstvisie Huisartsenzorg. Huisartsgeneeskunde voor ouderen. NHG, 2007. 31-5-2007.
2. Stek ML, Vinkers DJ, Gussekloo J, Beekman AT, van der Mast RC, Westendorp RG. Is depression in old age fatal only when people feel lonely? Am J Psychiatry 2005;162(1):178-180.
3. Perissinotto CM, Stijacic C, I, Covinsky KE. Loneliness in older persons: a predictor of functional decline and death. Arch Intern Med 2012;172(14):1078-1083.
4. Andrew MK, Mitnitski A, Kirkland SA, Rockwood K. The impact of social vulnerability on the survival of the fittest older adults. Age Ageing 2012;41(2):161-165.
5. Formiga F, Ferrer A, Chivite D et al. Serum high-density lipoprotein cholesterol levels correlate well with functional but not with cognitive status in 85-year-old subjects. J Nutr Health Aging 2012;16(5):449-453.
6. Ng TP, Aung KC, Feng L, Scherer SC, Yap KB. Homocysteine, folate, vitamin B-12, and physical function in older adults: cross-sectional findings from the Singapore Longitudinal Ageing Study. Am J Clin Nutr 2012;96(6):1362-1368.
7. Ford I, Mooijaart SP, Lloyd S et al. The inverse relationship between alanine aminotransferase in the normal range and adverse cardiovascular and non-cardiovascular outcomes. Int J Epidemiol 2011;40(6):1530-1538.
8. Schalk BW, Visser M, Deeg DJ, Bouter LM. Lower levels of serum albumin and total cholesterol and future decline in functional performance in older persons: the Longitudinal Aging Study Amsterdam. Age Ageing 2004;33(3):266-272.
9. Swart KM, van Schoor NM, Heymans MW, Schaap LA, den HM, Lips P. Elevated homocysteine levels are associated with low muscle strength and functional limitations in older persons. J Nutr Health Aging 2013;17(6):578-584.
10. Van Pottelbergh G., den Elzen WP, Degryse J, Gussekloo J. Prediction of mortality and functional decline by changes in eGFR in the very elderly: the Leiden 85-plus study. BMC Geriatr 2013;13:61.
11. den Elzen WP, Willems JM, Westendorp RG, de Craen AJ, Assendelft WJ, Gussekloo J. Effect of anemia and comorbidity on functional status and mortality in old age: results from the Leiden 85-plus Study. CMAJ 2009;181(3-4):151-157.
12. Cruz-Jentoft AJ, Baeyens JP, Bauer JM et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing 2010;39(4):412-423.
13. Morley JE, Baumgartner RN, Roubenoff R, Mayer J, Nair KS. Sarcopenia. J Lab Clin Med 2001;137(4):231-243.
14. Rolland Y, Czerwinski S, Abellan Van KG et al. Sarcopenia: its assessment, etiology, pathogenesis, consequences and future perspectives. J Nutr Health Aging 2008;12(7):433-450.
15. Fried LP, Tangen CM, Walston J et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56(3):M146-M156.
16. Wilson J, Jungner G. Principles and practice of screening for disease. World Health Organization, 1968
17. Beswick AD. Complex interventions to improve physical function and maintain independent living in elderly people: a systematic review and meta-analysis. 2008.
18. Lin JS, Whitlock EP, Eckstrom E et al. Challenges in synthesizing and interpreting the evidence from a systematic review of multifactorial interventions to prevent functional decline in older adults. J Am Geriatr Soc 2012;60(11):2157-2166.

19. de Jonge P, Huyse FJ, Stiefel FC. Case and care complexity in the medically ill. Med Clin North Am 2006;90(4):679-692.
20. De Staatssecretaris van Volksgezondheid Welzijn en Milieu, mw dr. J. Bussemaker. Brief aan de Tweede kamer: Multimorbiditeit en ouderenzorg. 12-11-2007.
21. Stuck AE, Egger M, Hammer A, Minder CE, Beck JC. Home visits to prevent nursing home admission and functional decline in elderly people: systematic review and meta-regression analysis. JAMA 2002;287(8):1022-1028.
22. Smelt AF, van der Weele GM, Blom JW, Gussekloo J, Assendelft WJ. How usual is usual care in pragmatic intervention studies in primary care? An overview of recent trials. Br J Gen Pract 2010;60(576):e305-e318.
23. KNMG. Sterke medische zorg voor kwetsbare ouderen. 2010.
24. Brown C, Lilford R. The stepped wedge trial design: a systematic review. BMC Medical Research Methodology 2006;6(1):54.
25. Lutomski JE, Baars MA, Schalk BW et al. The development of the Older Persons and Informal Caregivers Survey Minimum DataSet (TOPICS-MDS): a large-scale data sharing initiative. PLoS One 2013;8(12):e81673.
26. von Faber M, Bootsma-van der Wiel A, van Exel E et al. Successful aging in the oldest old: Who can be characterized as successfully aged? Arch Intern Med 2001;161(22):2694-2700.
27. Stolee P, Rockwood K, Fox RA, Streiner DL. The use of goal attainment scaling in a geriatric care setting. J Am Geriatr Soc 1992;40(6):574-578.
28. Gordon JE, Powell C, Rockwood K. Goal attainment scaling as a measure of clinically important change in nursing-home patients. Age Ageing 1999;28(3):275-281.
29. Iliffe S, Lenihan P, Orrell M, Walters K, Drennan V, Tai SS. The development of a short instrument to identify common unmet needs in older people in general practice. Br J Gen Pract 2004;54(509):914-918.
30. Wiegant E. Ouderenzorg: dan komt het écht aan op samenwerken. De dokter 2014;5(1):14-20.



10

SUMMARY

Chapter 1 is the general introduction to this thesis and describes proactive integrated care for older people in general practice. Integrated care was introduced in 2007 by the National Programme of Elderly Care (NPEC) and in 2008 by the Dutch College of General Practitioners (DCGP), as a response to poorly coordinated care for older people with complex problems in general practice.

Most older people have multiple functional, somatic, mental and social problems which often interact - these are generally covered by the umbrella term *complex problems*. Older people with complex problems might benefit from proactive integrated care.

However, before general practitioners (GPs) can provide integrated care to older people, they need to properly identify older people with complex problems. In the work presented in this thesis, we tested the feasibility of five methods to identify this group of older people in general practice. These measures included a profile of laboratory measurements, the Fried frailty phenotype criteria, the clinical intuition of the GP, the ISCOPE screening questionnaire, and muscle strength measured as handgrip and quadriceps strength. These five measures were selected because: 1) laboratory measurements are regularly used by GPs to monitor older persons, 2) Fried's frailty phenotype is an internationally recognized and validated measure, 3) most healthcare providers have a clear intuition about the vulnerability of older people, 4) the ISCOPE screening questionnaire is developed based on the definition of complex problems of the DCGP, and 5) hand grip and quadriceps strength are often used as a measure for sarcopenia (degenerative loss of skeletal muscle often associated with poor health outcomes) Therefore, all these measures might be effective in the aim to identify complex problems in general practice.

Primary care for older people with complex problems is sometimes sub-optimal because multiple (medical) specialists and (informal) caregivers are involved, and disease-specific guidelines do not always apply to older people with complex problems. To optimally address these complex problems it is suggested that GPs, medical specialists and (informal) caregivers should collaborate – this is known as *integrated care*. However, to our knowledge, when the research described in this thesis was started, no programs were available for integrated primary care. Therefore, we selected a method that is commonly used by elderly care -, and rehabilitation physicians in the Netherlands and implemented this method in primary care. Specifically, to support this integrated approach, the GP/physician (who has overall responsibility) in close collaboration with other healthcare workers (e.g. physiotherapist, psychologist, etc.) formulates a care plan which combines problems on all major health domains (i.e. functional, somatic, mental and social). This care plan was used in a pragmatic randomized controlled trial as an integrated care intervention to test the hypothesis that older people with complex problems might benefit from integrated care.

In **Chapter 2** the dynamic nature of disability in the oldest old was studied. For this purpose, we used data from the Leiden 85-plus Study, a population-based study of 85-year-old individuals living in Leiden, the Netherlands. In this group, during the five-year follow-up, we examined transitions between disability states. A multi-state model was used to assess the risks of transitions between no disability, disability in instrumental activities of daily living (IADL disability), disability in basic activities of daily living (BADL disability), and death. At baseline, a large percentage of the population had IADL disability only, or IADL and BADL disability combined. During follow-up, an even larger percentage of the group made one or more transitions. Most of these transitions were directed to deterioration in disability, or death. We found that males had a lower risk of deterioration compared to females. The presence of depressive symptoms, chronic disease and cognitive impairment carried the highest risk of deterioration into disability. Based on these findings, we concluded that disability remains a dynamic process in the oldest old, with some older people experiencing a more rapid decline than others. These results are important, because the oldest old are the fastest growing segment of the general population. Therefore, these results might be used to develop preventive strategies directed towards disability. More studies are needed to further develop and implement these new strategies.

In **Chapter 3** we tested whether a combination of seven laboratory measurements has a better predictive accuracy in predicting mortality than gait speed and disability in IADL, which are other known predictors of mortality. This study was also embedded in the Leiden 85-plus Study. The seven laboratory measurements that were combined in a laboratory profile and were measured at baseline (age 85 years) were: high-density lipid cholesterol (HDL-C), albumin, alanine transaminase, hemoglobin, creatinine clearance homocysteine and C-reactive protein (CRP). These seven laboratory abnormalities were included as markers of different physiological systems; general health status (CRP), cardiovascular status (homocysteine), hematological status (hemoglobin), fatty acid metabolism (HDL-C), liver function (alanine transaminase), nutritional status (albumin), and renal function (creatinine clearance). It was found that 74% of our study population had one or more laboratory abnormalities at baseline and that an increasing number of abnormalities was associated with an increased mortality risk. Compared to low gait speed and disability in IADL, the predictive accuracy of the laboratory profile was similar. Therefore, the laboratory profile may be useful for clinicians as it provides information beyond age and sex. Moreover the laboratory profile is easily available, as most older people are regularly monitored by laboratory measurements. However, studies are needed to confirm these results in additional cohorts before implementation in clinical practice is possible. In addition, our study provides no etiological insight into the combinations of laboratory measurements; this is another topic for future studies.

In Chapter 2 it was found that functional, somatic and mental problems contribute to deterioration in disability. Most older people have problems not only on one domain, but on multiple domains. Therefore, in **Chapter 4** we explored whether combinations of health problems interact and whether this interaction is associated with indicators of poor health. i.e. disability, poor cognitive function, depressive symptoms, loneliness, health-related quality of life, and GP contact time. This study was embedded in the Integrated **C**are for **O**lder **PE**ople (ISCOPE) study (Chapter 8). All participants (aged 75 years and over) of the ISCOPE study filled out the ISCOPE screening questionnaire; this consists of 21 questions on four domains (functional, somatic, mental and social). During home visits, the participants were interviewed to obtain data on health indicators at baseline and again 12 months later. GP contact time was extracted via the electronic medical records of the participant's GPs. At baseline, over 80% of the participants had problems on more than one health domain. The number of health domains with problems was associated with poor health indicators, and problems on all four domains had an additional negative effect on these health indicators. At follow-up, an increased number of domains with problems was associated with an increased decline in health indicators, and the presence of problems on all four domains was associated with an additional negative effect on GP contact time. This implies that combinations of functional, somatic, mental and social problems interact, which may reflect the complexity of older individuals with problems on these domains. Future research should examine interventions for older people with problems on all four domains.

In chapter 4 it was shown that the ISCOPE screening questionnaire can be used to identify older people with complex problems. **Chapter 5** investigates whether the ISCOPE screening questionnaire is also a valid and feasible questionnaire to identify complex problems in older people in primary care**.** It was found that the feasibility of the questionnaire could indeed be improved, as the response rate was not satisfactory (63%). Moreover, several studies have reported that non-responders tend to have more problems than responders. This was also the case in our study, i.e. older people who did not respond were appraised as being 'vulnerable' by their GP more often and more often received home visits. Of the responders, 99% filled out the entire questionnaire, which resulted in a minimal number of missing values. To determine the internal consistency, Cronbach's alphas were calculated. These ranged from reasonable for the somatic (0.52) and mental domain (0.63) to good for the functional and social domain (0.81 and 0.70, respectively). Construct validity was evaluated by defining and testing 10 hypotheses about the associations of the four domains and the ISCOPE questionnaire, with adverse health indicators. All 10 hypotheses were confirmed, implying that the ISCOPE screening questionnaire has a good construct validity. To investigate the test-retest reliability, participants of five participating GPs were invited to fill out the questionnaire twice, within

two weeks. The test-retest reliability was highest for the functional domain (and the individual items within this domain) whereas the somatic domain had the lowest test-retest reliability. To determine the content validity, 16 geriatric experts agreed with the 21 original items of the ISCOPE screening questionnaire and suggested to add 11 items. These results imply that the ISCOPE screening questionnaire had a reasonable content validity. We conclude that the ISCOPE screening questionnaire is a short and reasonably feasible instrument, with satisfying clinimetric properties to identify complex problems in older people in primary care. Future research should investigate its responsiveness, generalizability and predictive validity. Moreover, the questionnaire needs to be further improved based on suggestions from the experts.

Apart from the ISCOPE screening questionnaire, other measures are available to identify complex problems. **Chapter 6** describes a study which compares the ISCOPE screening questionnaire with two of these measures, i.e. the Fried frailty phenotype criteria and the GP's clinical intuition regarding a patient's vulnerability. Frailty is a biologic syndrome of decreased reserves and resistance to stressors. According to the Fried frailty phenotype criteria, frailty arises when ≥ 3 of the following criteria are met: 1) unintentional weight loss, 2) self-reported exhaustion, 3) slow gait speed, 4) weak grip strength and 5) low level of physical activity. These latter criteria are often used in research but seldom in general practice, and never to identify older persons with complex problems. The GP and the older patient often have a long-term doctor-patient relationship and GPs often rely on a 'gut feeling' in their diagnostic process. However, although the clinical intuition of GPs has not yet been used as a measure for complex problems, GPs are known to take multiple domains into account, it is feasible that their intuition can be used as a measure to identify older persons with complex problems.

In a random sample of 823 participants aged ≥ 75 years (taken from all participants of the ISCOPE study) we compared the yield on health indicators (including disability, multimorbidity, depressive symptoms, quality of life, use of GP care) of these three measures (i.e. the ISCOPE questionnaire, the Fried frailty criteria, and GP's clinical intuition). Of the participants, over one third did not have complex problems according to the three measures. The remaining participants had complex problems, according to one, two or three of the measures. Irrespective of the measure, complex problems were associated with poor health indicators. When participants had complex problems according to two or three of the measures, the scores on these health indicators were even poorer. Of the three measures, the Fried frailty phenotype was most strongly associated with disability, whereas the ISCOPE screening questionnaire was most strongly associated with loneliness. However, from this study no clear conclusions can be drawn about the best instrument to use to identify complex problems in general practice. Therefore, the measure

of choice should perhaps depend on the intended intervention, as well as the workload and costs involved with each measure. In this study, the GP's clinical intuition was associated with poor health indicators and is, therefore, suitable to identify older people with complex problems; however, when GPs are interested in disability or loneliness, then they should combine this intuition measure with the Fried frailty phenotype or the ISCOPE questionnaire, respectively. Further studies are needed to establish whether the combination of multiple measures improves the identification of complex problems in general practice.

In **Chapter 7** we compared measurements of hand grip strength and quadriceps muscle strength (both as a measure for sarcopenia) for their association with poor health indicators. Because sarcopenia is thought to play a major role in functional impairment,, measures to identify sarcopenia could identify older people at risk for functional decline. These analyses were performed in a subpopulation of the ISCOPE study of 823 older participants (aged ≥ 75 years) of whom 764 had valid hand grip and quadriceps strength measurements. These participants were visited at baseline to measure hand grip and quadriceps strength. Data on poor health indicators were obtained at baseline and again 12 months later. It was found that, although the association between hand grip and quadriceps strength was weak, both measurements were independently associated with poor health indicators at baseline. Participants with both weak hand grip and weak quadriceps strength were identified as having the poorest scores on health indicators at baseline, compared to participants with normal hand grip and quadriceps strength and to participants who had only weak hand grip strength or weak quadriceps strength. At follow-up, weak hand grip strength was associated with quality of life and disability in basic activities of daily living. Quadriceps weakness did not contribute to the prediction of poor health indicators at 12 months follow-up. The conclusion drawn from this study is that the combination of handgrip strength and quadriceps strength may help to identify older people with complex problems in primary care.

The aim of **Chapter 8** was to investigate the introduction of an integrated care plan for older people (aged ≥75 years) with complex problems (identified with a postal questionnaire) in general practice. This was investigated within ISCOPE, which is a cluster randomized trial with 59 participating general practices (30 intervention practices, 29 control practices). Older people aged ≥75 years were screened with the ISCOPE screening questionnaire. Complex problems were defined as problems on ≥ 3 domains; 25% of the participants had complex problems. GPs from the intervention practices received training in making a care plan, and each GP made an integrated care plan for a random selection of 10 older persons with complex problems in his/her practice (resulting in a total number of 225 care plans). At 12 months follow-up there were no differences

in competence in the activities of daily living, quality of life and cost-effectiveness between the intervention and control group. Still, older patients with complex problems in the intervention group were slightly more satisfied with their GP. Moreover, GPs in the intervention group experienced better organization and more stability in the care for individual patients with complex problems. Therefore, the main conclusion drawn from this ISCOPE study is that GPs and older people with complex problems prefer a proactive integrated approach to geriatric care in general practice, but that this approach has no direct effect on functioning and quality of life of older people with complex problems, or on healthcare costs. There are several possible reasons for this lack of effect: 1) since the early 1990s, many changes have taken place in the care for older people in primary care. The present study started in a climate of growing interest in preventive and proactive care for older people, which ensured enthusiasm among the participating GPs - and government and healthcare professionals were already moving in this direction. GPs (also those in the control group) may have had increased awareness of the need to work proactively for their older patients, which might have caused dilution of the effect in the intervention group. 2) unsolicited care programs (or other devices) might not work because those who expect benefit from the offered service (or device) have already obtained it. 3) the intervention may have been too broad to cause an effect. 4) the intervention may not have been sufficiently intense to cause an effect. 5) a change in organization and/or delivery of care does not necessarily lead to an effect on the level of functioning and/or quality of life of the individual patient. 6) a randomized trial design may not be appropriate for this type of intervention, as it generally kind of as they consist of a complex mix of uncontrollable variables. Future research on integrated care interventions should take these points into consideration when setting up studies and planning integrated interventions. However, at the moment, there is no hard evidence for the effectiveness of integrated care for older people with complex problems in general practice.

In **Chapter 9**, we summarize and reflect on the main results of this thesis. In addition, we discuss implications for general practice and make some recommendations for further research. The results of this thesis shed new light on two important issues for evidence-based general practice care for older people: 1) the feasibility (or not) of the (proactive) identification of older people with complex problems and 2) the effectiveness (or not) of proactive integrated care for older people with complex problems in general practice.

We investigated five measures for their feasibility to identify older people with complex problems in general practice, i.e. a profile of laboratory measurements, handgrip and quadriceps muscle strength, Fried's frailty phenotype criteria, the clinical intuition of the GP, and the ISCOPE screening questionnaire. Each of these measures identified

different groups of older people with complex problems; moreover, the association between these five measures and health indicators also differed. Therefore, none of these measures can be specifically recommended as *the* gold standard. Even though all five measures identified a complex group of older people, based on the presents results we cannot recommend one of the measures as being the most feasible for general practice. As a result, the measure of choice in general practice could depend on the intended intervention of the GP, the workload involved with each measure, and the intention of the GP for a systematic inventory of the older population. In the ISCOPE study, systematic screening for complex problems was used to identify complex problems. We checked this systematic screening against the 10 Wilson and Jungner criteria for screening for disease; this revealed that systematic screening for complex problems fulfils 3 of the 10 Wilson and Jungner criteria. Since systematic population screening for complex problems is not yet appropriate another method is needed to identify older people with complex problems in general practice. Case finding involves screening of a smaller group of people based on the presence of known risk factors. This might prove to be an appropriate method to identify older people with complex problems.

In the ISCOPE study, a proactive integrated care plan did not have a direct effect on functional decline or quality of life among older people with complex problems. However, this does not mean that integrated care is not a good way to deal with older people with complex problems as- in fact, it has become a standard in some practices to the satisfaction of both GPs and their older patients. In addition to the reasons described in Chapter 8, the lack of effect of the ISCOPE study might also be attributed to the target group for integrated care. Older people with complex problems may have been too complex to show improvement in functioning. An intervention directed to older people at risk to become complex, might have had more a more obvious effect on these older people. Also, the sample size of the ISCOPE study may have been too small to demonstrate an effect. Therefore, an individual patient data meta-analysis of all studies in the context of the NPEC is recommended. The lack of effect of the ISCOPE study might also be due to the intervention, because unmet needs were not specifically considered in the integrated care plan. In addition, collaboration with elderly care physicians and GPs with expertise in geriatrics, might also improve integrated care in general practice. The above-mentioned items and recommendations could be used to design future studies and integrated care interventions for older people with complex problems in general practice.

In conclusion, the main findings emerging from this thesis are:

1) Older people with complex problems in general practice can be identified with relatively simple measures

2) No direct benefit from proactive integrated care for older people with complex problems can be demonstrated; this might be attributed to the study design used and/or to the intervention itself.

Based on the results of the work presented here, some recommendations can be made for a revision of the DCGP statement on the care for older people in general practice. Although we could not demonstrate a direct effect of integrated care for older people in general practice, this population warrants attention from GPs as they are at risk of adverse health outcomes. Future studies will reveal whether an intervention for older people at risk has some effect in the prevention of further deterioration. Our studies also provide evidence for the value of the clinical intuition of GPs regarding the 'vulnerability' of older people; this intuition can be used by GPs as a measure to identify older people with complex problems. Moreover, the four other measures that were investigated can also be used individually, or in combination, to identify these older people. Although we found no direct effect of integrated care on functional status or quality of life of these older people, in our opinion integrated care still remains the best type of care available for this specific group. We believe this is confirmed by the level of satisfaction of both older people and the GPs who were included in the intervention group of our ISCOPE study.



11

SAMENVATTING (DUTCH SUMMARY)

Door de toenemende levensverwachting en de vergrijzing veroudert de Nederlandse bevolking. Huisartsen krijgen daardoor steeds meer te maken met oudere patiënten. Een deel van deze ouderen zal vroeger of later geconfronteerd worden met 'complexe problematiek'. Het Nederlands Huisartsen Genootschap (NHG) definieerde complexe problematiek als volgt:

> *Bij complexe problematiek is sprake van een oudere persoon met één of meer van de volgende problemen die vaak met elkaar interacteren: cognitieve beperkingen, handicaps, psychosociale problematiek, multimorbiditeit, polyfarmacie en maatschappelijk isolement (alleen wonen, zonder of met weinig mantelzorg; eenzaamheid). Het gaat expliciet niet alleen om chronische zorg, maar ook om veelvoorkomende klachten/aandoeningen van ouderen (duizeligheid, slecht zien, horen, etc.)*
>
> *NHG standpunt huisartsgeneeskunde voor ouderen, 2007*

Omdat bij ouderen met complexe problematiek meerdere problemen tegelijk spelen, zijn vaak meerdere hulpverleners betrokken. Daarnaast zijn ziekte-specifieke richtlijnen vaak niet van toepassing voor deze ouderen omdat behandeling van het ene probleem vaak het andere probleem verergert of zelfs veroorzaakt. Het NHG-standpunt huisartsgeneeskunde voor ouderen stelt daarom dat samenhangende zorg noodzakelijk is voor ouderen met complexe problematiek. Samenhangende zorg wordt gedefinieerd als:

> *Een samenhangend geheel van zorginspanningen dat door verschillende (onafhankelijke) aanbieders onder een herkenbare regiefunctie wordt geleverd, waarbij het patiëntenproces centraal staat.*
>
> *NHG standpunt huisartsgeneeskunde voor ouderen, 2007*

Op het moment dat dit standpunt uitkwam, was er nog niet veel wetenschappelijk onderzoek gedaan naar de (kosten)effectiviteit van samenhangende zorg voor ouderen met complexe problematiek in de huisartsenpraktijk. In dit proefschrift worden een aantal uitgangspunten en aanbevelingen uit dit standpunt nader wetenschappelijk onderzocht. Niet alleen worden manieren om ouderen met complexe problematiek te identificeren beschreven, maar ook wordt het resultaat van een studie naar samenhangende zorg voor ouderen met complexe problematiek beschreven.

In **hoofdstuk 2** worden de resultaten gepresenteerd van een studie waarin het verloop van veranderingen in aanwezige beperkingen bij *activiteiten van het dagelijks leven* (ADL) onderzocht werd. Hiervoor werd gebruik gemaakt van de Leiden 85-plus Studie.

Dit is een prospectieve bevolkingsstudie van 85-jarigen die gedurende 5 jaar gevolgd zijn. Gedurende die 5 jaar werden jaarlijks *basis- en instrumentele activiteiten van het dagelijks leven* (respectievelijk afgekort als BADL en IADL) gemeten. Bij de start van de studie, op de leeftijd van 85 jaar, had een groot deel van de ouderen beperkingen in IADL of beperkingen in ADL en IADL. Gedurende de vijf jaar dat de deelnemers gevolgd werden, gingen de meeste deelnemers achteruit in ADL en IADL functioneren. Mannen hadden een lager risico op achteruitgang in hun functioneren. Ouderen die al beperkingen hadden, en ouderen met depressieve symptomen, chronische ziekten en cognitieve beperkingen hadden het hoogste risico op achteruitgang in functioneren. De conclusie van dit onderzoek is dat veranderingen in beperkingen veel voorkomen bij de oudste ouderen in de algemene populatie. Een belangrijke bevinding, want oudste ouderen zijn het snelst groeiende segment van de algemene populatie. Deze resultaten kunnen mogelijk gebruikt worden om preventieve strategieën te ontwikkelen om achteruitgang in beperkingen te voorkomen.

In **hoofdstuk 3** wordt een onderzoek beschreven naar de voorspellende waarde voor sterfte van een profiel met zeven laboratoriumwaarden. De voorspellende waarde van dit laboratoriumprofiel werd vergeleken met de voorspellende waarden van twee andere bekende voorspellers van sterfte (loopsnelheid en beperkingen in IADL). Voor deze studie werd wederom de Leiden 85-plus Studie gebruikt. De zeven laboratoriumwaarden die gebruikt werden voor het profiel waren *high density lipoprotein* (HDL) *cholesterol, albumine, alanine transaminase* (ALAT), *hemoglobine* (Hb), *creatinineklaring, C-reactive protein* (CRP) en *homocysteine*. Deze laboratoriumwaarden werden gekozen omdat ze een marker zijn van verschillende fysiologische systemen: vetmetabolisme (HDL-cholesterol), voedingsstatus (albumine), leverfunctie (ALAT), hematologische status (hemoglobine), nierfunctie (creatinineklaring), cardiovasculaire status (homocysteine) en algemene gezondheid (CRP). Deze zeven laboratoriumwaarden werden gemeten op de leeftijd van 85 jaar. De laboratoriumwaarden werden ingedeeld in geslachtsafhankelijke kwartielen. Het laagste kwartiel van HDL-cholesterol, albumine, ALAT, Hb en creatinineklaring en het hoogste kwartiel van CRP en homocysteine werden als afwijkend gedefinieerd. Van alle deelnemers had 74% één of meer laboratoriumafwijkingen op 85-jarige leeftijd. Het risico op sterfte nam toe naarmate het aantal laboratoriumafwijkingen toenam. De accuraatheid van de voorspelling van sterfte met het laboratoriumprofiel was vergelijkbaar met die van lage loopsnelheid of van beperkingen in IADL. Dit profiel is makkelijk te verkrijgen omdat laboratoriumwaarden van veel ouderen al regulier in de gaten worden gehouden. Om te onderzoeken of het profiel ook gebruikt kan worden voor het voorspellen van achteruitgang in functioneren is verder onderzoek nodig. Daarnaast is onderzoek in andere groepen ouderen nodig, zodat het profiel extern gevalideerd kan worden.

Uit hoofdstuk 2 bleek dat functionele, somatische en psychische problemen ieder een rol spelen bij achteruitgang in zelfredzaamheid. Vele ouderen kampen echter met verschillende ziekten en problemen, die tegelijkertijd of in samenhang met elkaar optreden (combinaties van functionele, somatische, psychische en sociale problemen), en mogelijk met elkaar interacteren. Daarom onderzochten we in **hoofdstuk 4** de gevolgen van de combinatie van functionele, somatische, psychische en sociale problemen voor ouderen in de huisartspraktijk. Deze problemen werden opgespoord middels de ISCOPE screeningsvragenlijst. ISCOPE staat voor de **I**ntegrated **S**ystematic **C**are for **O**lder **PE**ople (ISCOPE) studie. ISCOPE is een cluster gerandomiseerde trial met 59 deelnemende huisartsenpraktijken waarin ouderen (75+) gescreend werden op het bestaan van complexe problematiek met de ISCOPE screeningsvragenlijst. De ISCOPE screeningsvragenlijst bestaat uit 21 items, verdeeld over 4 domeinen (functioneel, somatisch, psychisch en sociaal). De gevolgen van het bestaan van problemen op één of meer domeinen hebben we gemeten met gezondheidsindicatoren, zoals zelfredzaamheid, cognitief functioneren, depressieve symptomen, eenzaamheid, kwaliteit van leven en huisartszorggebruik. Tijdens interviews werden de deelnemende ouderen tweemaal bevraagd over deze gezondheidsindicatoren, één maal bij de start van de studie en één maal 12 maanden na de start van het onderzoek. Vanuit het *Huisartsen Informatie Systeem* (HIS) werd informatie verkregen over het huisartszorggebruik van de deelnemers. Het aantal gezondheidsdomeinen met problemen op de ISCOPE screeningsvragenlijst was geassocieerd met verminderde zelfredzaamheid, cognitie, kwaliteit van leven en met meer depressieve symptomen, eenzaamheid en huisartszorggebruik, zowel bij de start van de studie als na 12 maanden. Voor problemen op alle vier de gezondheidsdomeinen werd een extra afname gevonden in zelfredzaamheid, cognitie en kwaliteit van leven en een extra toename van depressieve symptomen, eenzaamheid en zorggebruik. Deze resultaten bevestigen dat de domeinen onderling interacteren en dat ouderen met problemen op 4 domeinen de laagste scores op gezondheidsindicatoren hebben.

Uit hoofdstuk 4 bleek dat we met de ISCOPE screeningsvragenlijst in staat waren ouderen met complexe problematiek in de huisartspraktijk op te sporen. In **hoofdstuk 5** onderzochten we de uitvoerbaarheid en validiteit van deze vragenlijst. De uitvoerbaarheid van de vragenlijst was redelijk. Van de aangeschreven ouderen retourneerde 63% de vragenlijst. Het is bekend dat ouderen die niet reageren vaker complexe problematiek hebben dan respondenten. Uit een non-responsanalyse bleek dit ook in onze studie het geval, want we zagen dat diegenen die niet reageerden vaker kwetsbaar werden genoemd door de huisarts en daarnaast ook vaker door de huisarts thuis bezocht werden. Van de ouderen die reageerden vulde bijna 99% alle items in. De interne consistentie van de domeinen was hoog voor het functionele en het sociale domein (Cronbach's alpha 0,81 en 0,70, respectievelijk); de andere domeinen hadden een lagere interne con-

sistentie (somatische domein 0,52 en psychisch domein 0,63). Om de constructvaliditeit te bepalen, hebben we tien hypotheses getest. Uit Spearman's rangcorrelaties tussen de vragenlijst en gezondheidsindicatoren bleek dat alle tien de hypotheses bevestigd werden. De constructvaliditeit van de ISCOPE screeningsvragenlijst is daarmee als goed te kwalificeren. Uit een steekproef van de deelnemers die de vragenlijst tweemaal invulden, bleek dat de test-hertest betrouwbaarheid redelijk was (voor de aanwezigheid complexe problematiek, aantal domeinen met problemen en het somatische, psychische en het sociale domein) tot bijna perfect (voor de individuele vragen en het functionele domein). We bepaalden de inhoudsvaliditeit door 16 geriatrische experts te vragen commentaar te geven op de vragenlijst. De experts vonden het merendeel van de items relevant voor het domein dat werd gemeten, maar zij vonden de domeinen niet compleet. Zij raadden daarom aan om 11 items toe te voegen aan de vragenlijst. Al met al is de ISCOPE-vragenlijst een instrument met een redelijke uitvoerbaarheid en - validiteit en lijkt daarom een geschikt instrument om ouderen met complexe problematiek in de huisartsenpraktijk op te sporen. Er is echter nog ruimte voor verbetering indien de suggesties van de experts in de vragenlijst worden meegenomen. Daarnaast is er nog geen onderzoek gedaan naar de responsiviteit, generaliseerbaarheid en de predictieve validiteit van de vragenlijst. Ook het resultaat van dat onderzoek zou wellicht tot verbetering van de vragenlijst kunnen leiden. Een vervolgonderzoek op genoemde punten van de vragenlijst moet dit uitwijzen.

Naast de ISCOPE screeningsvragenlijst zijn er ook andere meetinstrumenten beschikbaar om complexe problematiek bij ouderen op te sporen. In **hoofdstuk 6** presenteren we onderzoek waarin de ISCOPE screeningsvragenlijst wordt vergeleken met twee andere meetinstrumenten, namelijk de Fried frailty phenotypecriteria en de klinische intuïtie van de huisarts. We vergeleken de geschiktheid van deze instrumenten met het oog op het opsporen van complexe problematiek door huisartsen in hun praktijk. Het Fried frailty phenotype spoort 'frailty' op bij ouderen. 'Frailty' is een biologisch syndroom van verminderde reservecapaciteit van de organen en weerstand voor stressoren. Volgens de Fried frailty phenotype criteria is een oudere 'frail' als hij/zij voldoet aan 3 of meer van de volgende criteria: 1) ongewenst gewichtsverlies, 2) zelf-gerapporteerde uitputting, 3) verminderde loopsnelheid, 4) verminderde knijpkracht en 5) een laag niveau van fysieke activiteit. Deze criteria worden vaak gebruikt in onderzoek, maar worden zelden gebruikt in de huisartsenpraktijk. Het is bekend dat huisartsen gewend zijn om te vertrouwen op hun pluis/niet pluis gevoel in de spreekkamer en dat dit van groot diagnostisch belang kan zijn. Bovendien is bekend dat zorgverleners die met ouderen werken een goede intuïtie hebben voor de al of niet kwetsbaarheid van hun patiënten. In onze studie vroegen we de huisarts, die de oudere vaak al langere tijd kent, om een intuïtief oordeel over de kwetsbaarheid van de ouderen in zijn praktijk. We onderzoch-

ten of dit oordeel gebruikt kan worden als meetinstrument voor complexe problematiek in de huisartsenpraktijk.

De resultaten van de 3 meetinstrumenten werden vergeleken in een steekproef van 821 deelnemers van de ISCOPE-studie. Met vragenlijsten, die als gezondheidsindicatoren werden gebruikt, werden *functioneren, depressieve symptomen, eenzaamheid* en *kwaliteit van leven* gemeten. Gegevens over huisartszorggebruik werden verkregen uit het HIS. Van de 823 deelnemers, had ruim één derde *geen* complexe problematiek volgens de drie genoemde de meetinstrumenten. De rest van de deelnemers had complexe problematiek: 51% had complexe problematiek volgens de ISCOPE-vragenlijst, 27% in de ogen van de huisarts en 34% volgens het frailty fenotype. Deze percentages overlappen omdat er ook mensen zijn die volgens meerdere instrumenten complexe problematiek hebben; 19% had complexe problematiek volgens 2 instrumenten en 10% had complexe problematiek volgens 3 instrumenten. Complexe problematiek was voor alle meetinstrumenten geassocieerd met meer chronische ziekten, verminderde zelfredzaamheid, verminderde cognitie, meer depressieve symptomen en een lagere kwaliteit van leven. De scores op deze gezondheidsindicatoren waren nog slechter naarmate deelnemers volgens meer instrumenten complexe problematiek hadden. Over het algemeen had het Fried frailty fenotype een sterkere associatie met verminderde zelfredzaamheid dan de andere twee meetinstrumenten. De ISCOPE-vragenlijst identificeerde eenzaamheid beter dan de andere twee instrumenten. Welk meetinstrument het meest geschikt is voor de huisartsenpraktijk is afhankelijk van de behoefte van de huisarts; bij de keuze van een instrument zou de huisarts rekening kunnen houden met de beoogde interventie, de tijdsinvestering en kosten van elk instrument. De klinische intuïtie van de huisarts bleek ook een goede methode om ouderen met complexe problematiek op te sporen, maar als de huisarts geïnteresseerd is in verminderde zelfredzaamheid of eenzaamheid kan de huisarts dit oordeel mogelijk beter combineren met respectievelijk het Fried frailty phenotype of de ISCOPE vragenlijst. Naar het combineren van meerdere instrumenten moet echter nog wel meer onderzoek worden gedaan.

In **hoofdstuk 7** worden handkracht en beenkracht vergeleken met betrekking tot gezondheidsindicatoren. De handkracht werd gemeten als handknijpkracht, de beenkracht als de kracht van de quadriceps-spier. Handkracht en beenkracht worden beiden beschouwd als een marker voor sarcopenie, dat een verlies van skeletspierweefsel op oudere leeftijd betekent. Omdat sarcopenie sterk is geassocieerd met achteruitgang in functioneren, zouden meetinstrumenten die sarcopenie meten mogelijk ook ouderen met complexe problematiek kunnen opsporen. We vergeleken daarom de resultaten van beide spierkrachtmetingen in een subgroep van 764 deelnemers van de ISCOPE-studie. Deze deelnemers werden thuis bezocht bij de start van de studie en na 12 maanden. Bij

de start van de studie werden beide spierkrachtmetingen verricht. Tijdens de bezoeken bij de start van de studie en na 12 maanden werden verdere gegevens verzameld over verschillende gezondheidsindicatoren. We vonden dat de associatie tussen handkracht en beenkracht zwak was. Toch waren beide spierkrachtmetingen geassocieerd met indicatoren van slechte gezondheid bij de start van de studie (zoals verminderde kwaliteit van leven, meer beperkingen in ADL, meer huisartszorggebruik en meer hospitalisatie). Deelnemers met zowel een zwakke handkracht als beenkracht hadden, bij de start van de studie, de slechtste scores op deze gezondheidsindicatoren. Zwakke handkracht aan de start was na 12 maanden geassocieerd met een verminderde kwaliteit van leven en beperkingen in ADL, Zwakke beenkracht droeg niet bij aan de voorspelling van slechte scores op gezondheidsindicatoren na 12 maanden. De belangrijkste conclusie van dit hoofdstuk is dat de combinatie van hand- en beenkracht metingen ouderen opspoort met de meest complexe problematiek, omdat deze ouderen de slechtste scores hadden op de gezondheidsindicatoren.

In **hoofdstuk 8** bestudeerden we de effecten op zelfredzaamheid en kwaliteit van leven van het invoeren van samenhangende zorg voor ouderen met complexe problematiek, die worden opgespoord met de ISCOPE screeningsvragenlijst in de huisartsenpraktijk. Aan ISCOPE deden 59 huisartspraktijken mee. Dertig praktijken werden geloot in de interventiegroep en 29 praktijken in de controlegroep. In alle deelnemende praktijken werden ouderen (75+) gescreend op de aanwezigheid van complexe problematiek met de ISCOPE screeningsvragenlijst. Complexe problematiek werd gedefinieerd als problemen op drie of vier van de vier domeinen. Na een training maakten de huisartsen in de interventiegroep een zorgplan voor 225 willekeurig geselecteerde deelnemers (10 per huisartsenpraktijk) met complexe problematiek. De controlepraktijken leverden de voor huisartsen gebruikelijke zorg. Na 12 maanden follow-up waren er geen verschillen in zelfredzaamheid in ADL, kwaliteit van leven en gezondheidszorgkosten tussen interventie- en controlegroep. Patiënten in de interventiegroep waren echter wel meer tevreden over hun huisarts. Daarnaast ervoeren huisartsen in de interventiegroep meer overzicht en stabiliteit in de zorg voor individuele patiënten met complexe problematiek. De belangrijkste conclusie van ISCOPE is daarom ook dat zowel huisartsen als hun patiënten met complexe problematiek baat hebben bij een proactieve samenhangende aanpak van de zorg voor ouderen met complexe problematiek in de huisartspraktijk, maar dat deze aanpak geen direct effect heeft op zelfredzaamheid en kwaliteit van leven van ouderen met complexe problematiek. De nieuwe aanpak is niet duurder maar ook niet goedkoper dan de huidige zorg. Voor het gebrek aan effect in onze studie zijn een aantal mogelijke redenen. Allereerst zijn er sinds de jaren negentig veel verbeteringen in de zorg voor ouderen doorgevoerd. Bovendien was toen onze studie startte veel aandacht voor preventieve en proactieve zorg voor ouderen. Dit kan er aan hebben bijgedragen

dat niet alleen de huisartsen in de interventiegroep, maar ook huisartsen in de controlegroep, samenhangende zorg hebben toegepast waardoor het moeilijk is geweest om een verschil te vinden tussen beide groepen. Ten tweede zijn zorgprogramma's waar patiënten niet om hebben gevraagd vaker niet effectief gebleken. Ten derde is onze interventie misschien gericht geweest op een te breed probleem en had deze interventie wel effect kunnen hebben als we ons op één risicofactor gericht hadden. Ten vierde is onze interventie mogelijk niet voldoende sterk geweest om een effect aan te tonen. Ten vijfde leidt een verandering in de aanpak in de organisatie van de zorg niet noodzakelijkerwijs tot effecten op het niveau van functioneren of kwaliteit van leven van de individuele oudere patiënt. Ten zesde is een gerandomiseerd onderzoek mogelijk niet geschikt voor dit soort interventies omdat deze erg complex in elkaar zitten en afhankelijk zijn van veel verschillende variabelen. Er zijn dus goede redenen voor het gebrek aan effect in onze studie. Mogelijk kunnen nieuwe studies op dit gebied deze redenen meenemen bij het opzetten en uitvoeren van de studie. Vooralsnog vinden wij dus echter geen bewijs voor samenhangende zorg voor ouderen in de huisartsenpraktijk.

In **hoofdstuk 9** worden de belangrijkste bevindingen van dit proefschrift beschreven en bediscussieerd. Aan de hand daarvan worden klinische aanbevelingen en aanbevelingen voor verder onderzoek gedaan. Het doel van dit proefschrift was het onderzoeken van meetinstrumenten om ouderen met complexe problematiek op te sporen in de huisartsenpraktijk. Daarnaast onderzochten we ook het effect van proactieve samenhangende zorg voor ouderen met complexe problematiek op zelfredzaamheid en kwaliteit van leven in de huisartsenpraktijk.

We hebben vijf meetinstrumenten onderzocht om ouderen met complexe problematiek op te sporen, namelijk een laboratoriumwaardenprofiel, hand- en beenkracht metingen, de ISCOPE screeningsvragenlijst, de Fried frailty phenotype criteria en de klinische intuïtie van de huisarts. Met elk van deze vijf meetinstrumenten waren we in staat om ouderen met complexe problematiek op te sporen en daarom zouden al deze methoden kunnen worden toegepast in de huisartsenpraktijk. Geen van deze instrumenten kon echter aangewezen worden als de 'gouden standaard' voor complexe problematiek. Het is op basis van onze onderzoeksresultaten ook niet nog mogelijk om een uitspraak te doen over het meetinstrument dat het meest geschikt is voor de huisartsenpraktijk. Bij de keuze van een instrument zou de huisarts rekening moeten houden met de beoogde interventie, de tijdsinvestering en kosten van elk instrument. Het hangt ook af van de vraag of de huisarts systematisch elke oudere in zijn praktijk in kaart wil brengen, of liever kiest voor een meetinstrument dat de huisarts op indicatie inzet bij ouderen als de huisarts vermoedt dat er complexe problematiek speelt. Verder is het de vraag of vroegopsporing voor complexe problematiek wel de juiste manier is geweest om ouderen

met complexe problematiek op te sporen, omdat zo'n programma moet voldoen aan de criteria van Wilson en Jungner. Vroegopsporing voor complexe problematiek voldoet vooralsnog niet aan deze criteria. Mogelijk is case-finding een betere manier om deze populatie in de toekomst op te sporen.

Wij vonden in de ISCOPE studie dat systematische screening voor complexe problematiek gevolgd door een proactief samenhangend zorgplan voor ouderen met complexe problematiek in de huisartsenpraktijk geen direct effect had op zelfredzaamheid, kwaliteit van leven en gezondheidszorgkosten. Samenhangende zorg hoeft echter niet meteen helemaal te worden afgeschreven. Er zijn namelijk al veel huisartsenpraktijken waar samenhangende zorg naar tevredenheid wordt toegepast. Naast de mogelijke verklaringen voor de afwezigheid van een effect zoals beschreven in hoofdstuk 8, zou dat gebrek aan effect ook nog verklaard kunnen worden uit een verkeerd gekozen doelgroep voor de interventie. In dat geval kan meer winst behaald worden bij ouderen die nog geen complexe problematiek hebben, maar risico lopen om complexe problematiek te krijgen. Ook een te kleine steekproefgrootte kan hebben bijgedragen aan het gebrek aan effect. Mogelijk is de interventie die in de ISCOPE studie werd gekozen ook niet de juiste om het effect van samenhangende zorg aan te tonen, want binnen ISCOPE werden de zogenoemde 'unmet needs' niet opgespoord, terwijl deze vaak groot effect hebben op de zelfredzaamheid en de kwaliteit van leven van ouderen met complexe problematiek. Dit alles zou kunnen worden meegenomen bij het opzetten van toekomstige studies en samenhangende zorginterventies voor ouderen met complexe problematiek. Hierbij kan samenwerking met een specialist ouderengeneeskunde of een kaderhuisarts ouderengeneeskunde mogelijk ook bijdragen aan meer samenhangende zorg in de eerste lijn.

Concluderend zijn de belangrijke bevindingen van dit proefschrift

1) Ouderen met complexe problematiek in de huisartsenpraktijk kunnen worden opgespoord met betrekkelijk simpele meetinstrumenten.
2) Er is geen direct effect aantoonbaar van samenhangende zorg voor ouderen met complexe problematiek in de huisartsenpraktijk.

Op basis van de resultaten van dit proefschrift kunnen we een aantal aanbevelingen doen voor een revisie van het NHG-standpunt ouderengeneeskunde: hoewel er geen direct effect aantoonbaar is van samenhangende zorg voor ouderen met complexe problematiek in de huisartsenpraktijk, verdient deze groep ouderen nog steeds de aandacht van huisartsen, omdat uit dit proefschrift blijkt dat deze groep risico loopt op ongewenste gezondheidsuitkomsten. Mogelijk moeten huisartsen al eerder ingrijpen, bij ouderen die risico lopen om complexe problematiek te ontwikkelen. Verder onder-

zoek zal moeten uitwijzen of dit zinvol is. Verder blijkt uit dit proefschrift dat de huisarts met zijn eigen klinische intuïtie in staat is om ouderen met complexe problematiek op te sporen. Daarnaast zijn er vier andere meetinstrumenten die de huisarts individueel of in combinatie zou kunnen gebruiken voor de opsporing van deze groep ouderen. Ook al is er geen direct effect van samenhangende zorg op de zelfredzaamheid of de kwaliteit van leven van ouderen, deze vorm van zorg blijft naar onze mening nog steeds het beste wat we deze groep kunnen bieden. De tevredenheid van zowel de ouderen als de huisartsen in ons onderzoek bevestigt dit.



APPENDICES



APPENDIX 1: ISCOPE SCREENING QUESTIONNAIRE

This questionnaire concerns your situation during the last month.
It consists of 26 short questions that may sometimes seem rather similar.
Please answer each question with the option that best fits your own situation.

Please use a blue or black pen

Correct / Right
Incorrect /Wrong

If you make a mistake and would like to correct it, cross the wrong answer out and mark the correct answer. If you have any doubt about an answer or question, try to give the answer that you find the most suitable.

For this study it is important that you answer ALL the questions.

PLEASE NOTE: the questionnaire is double-sided; the reverse side of the pages also contains questions.

Thank you very much for completing this questionnaire.

If you have any questions or comments please contact the Department of Public Health and Primary care of the LUMC, telephone ….

What is today's date?
What is your date of birth?
What is your gender? male/female

Daily life abilities
These first questions relate to how you function/manage your day-to-day life.
You may be helped in these activities by aids such as a stick, walking frame, or wheelchair.

1. Can you do the shopping without help from anyone else?

2. Can you walk outdoors without help from anyone else?

3. Can you dress and undress yourself without help from anyone else?
4. Can you go to the toilet without help from anyone else?

5. Can you manage your finances yourself (collect your money, pay your bills)?

6. How well would you say you cope with your general day-to-day life?

Well / average / not at all well

Health and illness

7. Which mark would you give for your physical fitness?

1	2	3	4	5	6	7	8	9	10
Not at all fit									Very fit

8. Do you experience day-to-day problems due to poor eyesight (even if you wear glasses or contact lenses)?

9. Do you experience day-to-day problems due to poor hearing (even if you wear a hearing aid)?

10. Do you experience problems with incontinence of urine or stools?

11. Do you experience daily problems due to pain?

12. Have you lost weight (more than 6 kg) in the last 6 months unintentionally?

13. Are you using more than 4 different kinds of medicine at the moment?

14. Have you had a fall in the last month?

15. Have you been admitted to the hospital in the last 6 months?

Psychological functioning

16. Do you feel you have memory complaints?

17. Have you recently felt sad or depressed?

18. Have you recently felt nervous or anxious?

19. Do you feel pretty worthless at the moment?

Social functioning

20. Do you experience emptiness in your life?

21. Do you feel the lack of a close friend?

22. Do you feel left alone sometimes?

23. Do you feel there are enough people with whom you feel a close connection?

24. Do you receive help from anybody in your immediate surroundings because you are unable to do things for yourself?

25. Has anybody helped you to fill in this questionnaire?

No, I have filled in the questionnaire myself.
Yes, someone helped me to answer these questions.
Somebody has answered them for me.

26. At the moment, which conditions limit you the most in your day-to-day life?

Explanation:

APPENDIX 2: ADDITIONAL ITEMS SUGGESTED BY THE EXPERTS

Suggested items by experts

Suggested item	Number of experts suggesting addition of this item	Item of the original questionnaire to be replaced	Number of experts suggesting replacement
Functional domain (7 items)			
bathing independently	4	shopping	1
cooking	2		
use of conveyance / travelling	2	managing finances	1
use of communication/telephone	2	walking outdoors	2
getting out of bed independently	1		
standing up from a chair independently	1		
managing medication	1	managing finances	1
coping with incontinence	1	going to the toilet	1
Somatic domain (13 items)			
incontinence	4		
making yourself understood	4	hearing	1
monitoring by general practitioner	1		
visited a doctor recently	1	hospital admission	1
climbing 15 steps	1	physical fitness	1
spontaneous bruising	1		
dizziness	1		
monitoring by medical specialist	1	hospital admission	1
use of walking aids	1		
use of communication	1		
ability to speak clearly	1		
fear of falling	1		
appetite			
Mental domain (3 items)			
level of autonomy	1		
fear of falling	1	worthless	1
recently lost a loved one	1	worthless	2
Social domain (7 items)			
satisfactory contacts with acquaintances or friends	2	emptiness/left alone	2/1
number of contacts per day	1	close connection to people	2
need for daily assistance	1		
recently visited someone/been visited by someone	1	close connection to people	1
social participation	1	close connection to people	1
someone available to help	1		
do you feel others take advantage of you	1		

APPENDIX 3: FRAMEWORK AND CONTENT OF THE TRAINING OF THE INTERVENTION GROUP OF THE ISCOPE STUDY

Background

The training was based on a program developed for the 'Professional Training program for GPs with expertise in Geriatrics' (supervised by the Dutch College of General Practitioners). During the training both general practitioners (GPs) and practice nurses joined the same group. Different learning styles were facilitated by using various teaching methods: theory, case discussions, reflection on group discussion, and planning the intervention in own practice.

First meeting

Introduction (30 min)

- Background of the ISCOPE study
- Results from the pilot study
- Questions

Individual care plan for older people with complex problems (50 min)

- Theory on the care plan
- Making a care plan for one older patient (in small groups)
- Discussion on the care plans in the whole group

Action plan for own practice (40 min)

- Routines in practice until now
- What can you learn from other practices?
- Schedule for planning 10 care plans for complex patients

Questions and homework for next meeting (30 min)

Second meeting

Experiences until now (30 min)

Individual care plan for 'own' older patient (40 min)

- With information from the electronic patient register and contextual information, the GPs and practice nurses make a care plan for one older patient in their practice

Action plan for own practice (40 min)

Questions/discussion (30 min)

Points of attention to start in own practice
- Register screening results in database
- Set up 1 care plan per week:
    - o Plan time to make the problem list
    - o Invite older people with complex problems to the practice
    - o Make the care plan
- Contact with other care professionals
- Plan evaluation
- Organize listing of community resources; look for resources for older people
- Don't forget living and social care resources
- Organization in own practice:
    - o Allocation of duties
    - o Assistance from geriatric specialist needed?
    - o More training or resources needed?
    - o How to register data in the computer

Third meeting

Aim: to develop an overview of resources in primary care, for the care for psychosocial problems and falls of older people.

Introduction, showing figures and results on psychosocial problems and falls, from the ISCOPE-study so far (20 min).

Discussion about practice guideline 'care for older people' of the Dutch College for General Practice, and the necessary contents of an overview of resources (20 min).

Work together with practice staff to set up an overview for own practice (40 min).

Discuss the results with other groups, exchange ideas (20 min).

Presentation and discussion with occupational therapist about care offered by the occupational therapist for older people with falls (40 min).

APPENDIX 4: FORMAT OF CARE PLAN BY THE GENERAL PRACTITIONER FOR OLDER PEOPLE WITH COMPLEX PROBLEMS

Older people with complex problems demand a special, pro-active approach of you as a general practitioner or practice nurse. (Statement for elderly care of the Dutch College of General Practice). For patients with multimorbidity a disease-oriented approach is insufficient. Using a patient-centered approach focusing on maintaining, restoring or maximizing function, quality of life and the ability to be independent in daily living is a more beneficial approach. Pro-active care means estimating the risk of deterioration and offering interventions that diminish those risks.

Key words in this process are: anticipate, delegate, evaluate.

This card contains tools to shape the care for older people with complex problems.

(SASPC model: Somatic, Functional, Social, Psychological and Communicative)[1]

As a first step: make an overview of the limitations and problems in the different areas of life. Prioritize them: which problems are most urgent for the older person herself/himself and for the informal caregivers?

Problemlist of patient…….

Health area	*Problem*	*Urgency*
Somatic		
Somatic		
Activities of daily living		
Activities of daily living		
Social		
Social		
Psychological		
Psychological		
Communicative		
Communicative		

1 Hertogh CMPM, Deerenberg-Kessler W, Ribbe MW. The problem-oriented multidisciplinary approach in Dutch nursing home care. Clin Rehabil. 1996; **10**:135-142

Care plan

The care plan brings coherence in the care process and is a means to direct care. The care plan is constructed by the general practitioner or practice nurse together with the older person and informal caregivers or relatives in cooperation with other caregivers

(nurse, physiotherapist, etc). A main aim is determined: maintain or restore function or is deterioration inevitable? Problems are organized in order of urgency and, per problem, a feasible aim is determined as well as the preferred intervention and evaluation date. Decide who does what and who will be the coordinator.

Care plan for……
Main aim……..
Case manager……..…….Care coordinator……

Problem	Aim	Action GP care (what, who)	Action other caregivers (what, who)	Evaluation

As an acronym for the steps to be taken in the pro-active care for older people with complex problems you can use FREDIE: Functioning, Reflect with the patient, Estimate risks, Determine aims, plan and perform Interventions, Evaluate.

APPENDIX 5: ECONOMIC EVALUATION ISCOPE STUDY

Methods

Costs were estimated from a health care perspective, with a one-year time horizon, at the price level of 2013. Normal GP contacts and medication use were derived from the electronic patient records of the participants. Out-of-hours GP contacts and other health care were derived from the Minimal Data Set of the National Program for Elderly Care collected during the home visits.[1] A detailed cost price analysis was performed for the training costs and the intervention costs for the proactive care. Other health care was valued using standard prices, designed to reflect societal costs and to standardize economic evaluations.[2]

For the economic evaluation, effectiveness was estimated in terms of 1-year quality-adjusted life years (QALYs). These QALYs were estimated using the Dutch tariff for the EuroQol classification system (EQ5D), measured at baseline, and at 6 months and 12 months.[3] As secondary analysis, QALYs were estimated using a visual analogue scale (VAS) ranging from 0 (worst imaginable health) to 100 (perfect health). VAS measurements were obtained at baseline and at 12 months and were transformed to a utility scale using the power transformation $1-(1-VAS/100)^{1.61}$.[4]

Cost-effectiveness acceptability curves were used to explicitly relate the difference in costs to the difference in QALYs. Depending on the willingness to pay (WTP) per QALY, acceptability curves show the probability that the experimental policy has a more favorable net benefit ($NB = WTP \times QALYs - Costs$) than the control policy.[5] Acceptability curves were estimated using bootstrapping. Missing data on health care use and utilities were accounted for using multiple imputation (using chained equations, with utilities, sex, age and randomization group as predictors).

Results

Costs for the care plans were estimated at €5900 for a practice with 25 older patients with care plans, or €236 per care plan (Table 1). Of these costs, 16% was for training GPs and practice nurses, 21% to identify people with complex problems (screening), 30% to make the care plans and 34% to carry out the care plans. The costs for the care plans are variable with the number of care plans, but the costs for training and screening are relatively fixed. As a result, for a practice with 10 care plans, costs per care plan would increase to €370.

With the exception of the care plans, no differences in health care use were found (Table 2). The costs of the care plan were low compared to (the variability of) the total costs during the 1-year follow-up period. As a result, total costs were not significantly different between the randomization groups. Also, effectiveness in terms of QALYs was not significantly different. For reasonable willingness to pay (values above €10,000 per

QALY), both policies are about 50% likely to be preferred (Figure 1). Due to this uncertainty, the economic preference for the proactive approach or usual care is undecided.

Table 1. Estimated training and intervention costs of proactive, goal-oriented, integrated care.

	Time (hours)	Costs* (in €)
Training costs		
Course development and preparation	46	6400
Communication with course participants	26	3600
Course materials		1000
Trainer's time for 22 training sessions	66	9200
Trainee's time for 65 trainees	357	35700
Total training costs for 65 trainees	495	55900
Costs per trainee		860
Intervention costs		
Training costs (1.1 trainee per practice)		950
Screening GP files and preparing letters	4	150
Postage letters to 150 older persons		300
Time invested by 100 older persons	50	500
Assessment of 100 questionnaires	8	300
Formulating 25 care plans by GP and practice nurse	25	1750
Executing 25 care plans by GP and practice nurse	25	1750
Executing 25 care plans by older persons	25	250
Total intervention costs for one practice with 25 care plans†	137	5900
Costs per care plan		236

Time was valued at €140 per hour for trainers and GPs, €36 per hour for practice nurses, and €10 per hour for older persons

† I.e., assuming that in a real-life setting more care plans would be made than in the current research setting

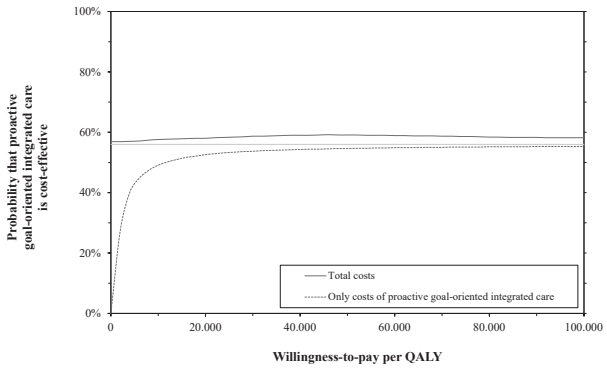


Figure 1. Cost-Effectiveness acceptability curve (i.e. the probability that proactive goal-oriented integrated care is cost effective compared to usual care, based on costs and EQ5D-based QALYs).

Table 2. Average health economic outcomes during the 1-year follow-up (based on intention-to-treat principle).

	Intervention group n=288	Control group n=1091	Difference (95% CI)		p-value
QALYs					
Based on EQ5D	0·554	0·534	0·020	(-0·359; 0·399)	0·92
Based on VAS	0·735	0·686	0·049	(-0·365; 0·462)	0·82
Health care use					
Care plan*	78%	0%	78%	(76%; 81%)	<0·001
Out-of-hours GP contacts (n)	0·3	0·3	0·0	(-1·0; 1·1)	0·91
Other GP contacts (n)	15·5	14·0	1·5	(-1·3; 4·3)	0·29
Medication*	100%	99%	1%	(-13%; 14%)	0·93
Days in hospital (d)	2·1	2·7	-0·7	(-3·9; 2·5)	0·68
Days in hospital day care (d)	1·1	1·8	-0·7	(-23·9; 22·6)	0·96
Days in residential home (d)	38·2	48·6	-10·4	(-48·2; 17·3)	0·59
Days in nursing home (d)	7·2	6·1	1·1	(-6·4; 8·5)	0·78
Days in day care (d)	7·8	6·8	1·0	(-24·5; 26·5)	0·94
Hours home care (h)	137	140	-2	(-128; 123)	0·97
Hours informal care (h)	280	292	-11	(-185; 163)	0·90
Health care costs (in €)					
Care plan	184	0	184	(181; 187)	<0·001
Out-of-hours GP contacts	16	14	3	(-39; 44)	0·90
Other GP contacts	604	557	47	(-97; 191)	0·52
Medication	1651	1623	28	(-243; 300)	0·84
Hospital	1025	1357	-332	(-1750; 1086)	0·65
Hospital day care	303	485	-182	(-6494; 6129)	0·96
Residential home	3728	4746	-1018	(-4664; 2629)	0·58
Nursing home	1850	1572	279	(-1496; 2054)	0·76
Day care	383	333	50	(-1189; 1288)	0·94
Home care	5976	6215	-239	(-8236; 7758)	0·95
Informal care	3040	3162	-122	(-2007; 1762)	0·90
Total costs	18761	20066	-1305	(-16349; 13744)	0·87

*percentage of patients

References

1 Lutomski JE, Baars MA, Schalk BW, et al;TOPICS-MDS Consortium. The Development of the Older Persons and Informal Caregivers Survey Minimum DataSet (TOPICS-MDS): A Large-Scale Data Sharing Initiative. PLoS One. 2013 Dec 4;**8**:e81673.

2 Hakkaart-van Roijen L, Tan SS, Bouwmans CAM. Manual for cost analyses, methods and standard prices for economic evaluations in health care (in Dutch). 2010. Dutch Health Insurance Executive Board.

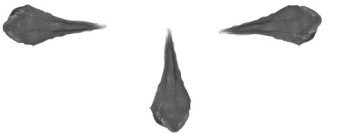
3 Lamers LM, Stalmeier PF, McDonnell J, Krabbe PF, Van Busschbach JJ. Measuring quality of life in economic evaluations: the Dutch EQ-5D tariff (in Dutch). Ned.Tijdschr.Geneeskd. 2005; **149**: 1574-1578.

4 Stiggelbout AM, Eijkemans MJ, Kiebert GM, Kievit J, Leer JW, Haes HJd. The 'utility' of the visual analog scale in medical decision making and technology assessment. Is it an alternative to the time trade-off? Int J Technol Assess Health Care 1996; **12**:291-298.

5 Zethraeus N, Johannesson M, Jonsson B, Lothgren M, Tambour M. Advantages of using the net-benefit approach for analysing uncertainty in economic evaluation studies. Pharmacoeconomics 2003;**21**:39-48.



DANKWOORD & CURRICULUM VITAE



DANKWOORD

Velen hebben bijgedragen aan de totstandkoming van dit proefschrift en een aantal van hen wil ik hier graag bij naam noemen.

Zonder de deelnemers van de Leiden 85-plus Studie en de deelnemers en deelnemende huisartsen van de ISCOPE-studie was dit proefschrift nooit tot stand gekomen. Ik ben, zowel de deelnemers als hun huisartsen, daarom dankbaar voor hun openhartigheid en bereidwilligheid.

Mijn promotor Jacobijn Gussekloo en copromotoren Jeanet Blom en Wendy den Elzen hebben mij met veel geduld begeleid bij mijn eerste stappen op het wetenschappelijke pad. Ook in een tijd dat werk en wetenschap even geen prioriteit waren, waren zij zeer coulant en meelevend. Ik ben hen daar zeer erkentelijk voor.

De ISCOPE-studie was een erg omvangrijke project. Er was veel mankracht nodig om de duizenden brieven te versturen en deelnemers te bellen en te bezoeken. Daarom wil ik de inzet van de onderzoeksmedewerkers en secretaresses van de afdeling Public Health en Eerstelijnsgeneeskunde (PHEG) niet onvermeld laten, want ik ben hen voor al dit werk veel dank verschuldigd.

Hoewel ze steeds wisselden, hadden ze 1 ding gemeen: 'gedeelde smart is halve smart' en 'gedeeld succes is dubbel zo groot': mijn kamergenoten op V6, V7, J9, P0 en nog eens V6; fijn dat ik smarten en successen met jullie mocht en kon delen! In het bijzonder noem ik: Paulette Egberts, al lang geen kamergenoot meer, maar nog steeds een grote steun in het afmaken van dit onderzoek en daarbuiten; Margot Heijmans die als huisarts een groot voorbeeld voor me is en met wie ik graag praat over onze ideeën over ouderenzorg en Annemarije Kruis die ook in 2011 begon met de huisartsopleiding en daardoor zowel in het wetenschappelijke als in het klinische een fijne sparringspartner is. Alle andere onderzoekers en collega's van de kerntaakgroep Wetenschappelijk Onderzoek van de afdeling PHEG wil ik danken voor hun collegialiteit.

De combinatie van promotie-onderzoek en de huisartsopleiding is een mooie uitdaging. Daarvoor ben ik dank verschuldigd aan mijn werkgever, de SBOH, die deze combinatie mede mogelijk maakte. Mijn opleiders Gertjan Bénit en Henk Immerzeel hebben mij geholpen om de opleiding met goed gevolg te doorlopen en tegelijkertijd de ruimte gegeven om dit proefschrift af te ronden, veel dank daarvoor.

Graag dank ik op deze plek Emma Stukart die de prachtige omslag van dit proefschrift ontwierp, en Edwin Thoen voor de hulp met het Venndiagram uit hoofdstuk 6.

Mijn dank gaat uit naar mijn vrienden en vriendinnen, waarvan ik er drie expliciet wil noemen. Allereerst Jolijn Trietsch en Willemien van de Water. Ik heb het prettig gevonden om met hen te kunnen discussiëren over het doen van een promotie-onderzoek in het LUMC. En natuurlijk Daphne van Embden, mijn paranimf, waarmee ik al sinds onze

tijd aan het Karolinska institutet de interesse en de passie voor de geneeskunde deel. Ik vind het bijzonder dat we mijn wetenschappelijke 'studie' op deze manier samen kunnen afsluiten.

Mijn broer Gijs wil ik danken voor het meelezen van de discussie, maar vooral omdat hij mijn paranimf is. Mijn broer Thomas wil ik bedanken voor zijn hulp met scannen van vragenlijsten. Zijn vriendin Dieneke Boer dank ik voor het meelezen en checken van de Engelse samenvatting van dit proefschrift.

Mijn vader wil ik danken voor het redigeren van de Nederlandse samenvatting en de aanmoedigingen om vooral door te zetten. Helaas heeft mijn moeder de voltooiing van dit proefschrift niet mee mogen maken. Zij is degene geweest die mijn interesse in ouderen aanwakkerde en ik ben erg blij dat ze dat gedaan heeft.

En als laatste dank ik natuurlijk Toine Hazen voor zijn hulp en steun bij het structureren van mijn gedachten en omdat hij altijd tijd voor me maakt. Heel, heel veel dank daarvoor!

CURRICULUM VITAE

Anne van Houwelingen was born on October 2nd, 1983 in Middelburg, the Netherlands. After passing her gymnasium exam in 2002, she studied Medicine at the Leiden University Medical Center (LUMC) from 2002 through 2008. In 2003, she participated in the exchange program of the LUMC with Karolinska Institutet in Stockholm, Sweden.

In 2009, she started as a PhD student at the research project described in this thesis at the department of Public Health and Primary Care of the LUMC, under supervision of dr. W.P.J. den Elzen, dr. J.W. Blom and prof. dr. J. Gussekloo. In 2011, she started with the the general practitioner vocational training and combined this with her PhD project.

At present, she is in her third year of this vocational training, which she aims to finish in 2016.

