Frailty screening in older patients in primary care using routine care data

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Screening op kwetsbaarheid bij oudere patiënten in de huisartsenpraktijk met behulp van routinezorgdata

(met een samenvatting in het Nederlands)

Proefschrift

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Table of contents

Chapter 1

General introduction

Ageing of the population and the frailty concept

Worldwide, the population is ageing. In the Netherlands, the population aged 65 years or older will increase from 2 million in 2012 to 4.7 million people in 2060.[1] A substantial number of these older people will experience a range of health problems. For example, 20% of people aged 65 to 74 years old and 30% of people aged 75 years or older have multimorbidity.[2] On average, 40% of older people report one or more disabilities, and in most domains, for example, the physical or social domain, older people report lower quality of life.[3,4]

These figures are based on population data, but not all older individuals will experience health problems and functional decline to the same extent. Whereas one 60-year-old individual might already suffer from multiple chronic diseases and experience major disabilities, a 90-year-old neighbour might be able to continue a normal life without limitations. To identify those older people most at risk of future health and social problems, the concept of frailty has been introduced.[5] Recently, in a consensus statement, 152 experts defined frailty as a condition characterised by decreased homeostatic reserves and diminished resistance to stressors, resulting in increased risk of adverse health outcomes.[6] The loss of reserve is caused by impairments in multiple inter-related physiological systems.[7] Some authors have defined frailty as increased vulnerability to adverse health outcomes, compared specifically to people of the same age.[3,8]

Primary care for frail older patients: transition from a reactive to a proactive approach

Most of the care needs of frail older people will be addressed in primary health care. As the gatekeepers to the healthcare system, general practitioners (GPs) resolve more than 90% of the health problems in the overall population.[9] Given their easy accessibility, their long-lasting relationships with their patients, and their integrated, patient-centred approach, GPs play a key role in the provision and coordination of care for frail older patients.[8,10]

The increased number of frail older people in the future poses a major burden on healthcare resources.[11,12] Currently, care for older people in general practice is provided in short consultations (10-15 minutes) by GPs, addressing (semi-)acute complaints or chronic diseases on an individual basis. This traditional approach to care provision is inadequate in vulnerable older patients. In a focus group study in the United Kingdom, GPs and practice nurses reported difficulties in managing patients with multimorbidity in the consultation time available.[13] Coordination of care, the support of self-management,

and identification of the patients' needs were reported as aims in care for older people that could not be met. A cross-sectional evaluation of primary care visits in the United States demonstrated that the mean consultation time for older patients with multimorbidity and polypharmacy did not differ from that of younger patients without these conditions, raising the question of whether the complex care needs of the former group received sufficient attention.[14] Moreover, in primary care, only half of the care that is recommended according to professional guidelines is actually provided.[15] When confronted with the broad spectrum of interacting medical and social problems of frail older patients, GPs often focus on the single illness that is perceived as the most important, instead of maintaining a holistic view.[8]

In a focus group study in Belgium, GPs reported that full compliance with all of the recommended evidence-based guidelines often induced polypharmacy in frail older people with multiple chronic diseases.[16] GPs are aware that polypharmacy increases the risk of non-compliance with drug intake, preventable medication-related hospital admissions, and other adverse health outcomes.[17,18] However, in current daily clinical practice, GPs find it difficult to maintain an overview of the exact medication intake, for which they require organisation and decision support.[19]

In conclusion, due to its current reactive organisation, primary care for frail older people is currently often inadequate. This inadequacy leads to unnecessary disease burden, avoidable acute derailments and hospitalisations, and high societal costs.[8] Therefore, a paradigm shift in primary care for older people is necessary, from reactive care for individual patients to a more proactive care provision based on frailty risk identification among older patients.[15,20,21]

Panel management as an example of proactive primary care

One of the ways to implement proactive primary care for older people is by the introduction of so-called "panel management", defined as a structured process for proactively identifying and addressing care needs, based on risk identification in the patient population.[22] A prerequisite for panel management is the presence of an electronic medical record (EMR) data registry, which allows a software application to perform electronic searches for risk factors in patients' clinical data. After screening the EMR data, the software reports on the population at risk and the actions that are required, based on current standards and guidelines.[15] By structurally reviewing the reminders for scheduled or overdue diagnostic, preventive or therapeutic actions, GPs or practice nurses can systematically address the health needs of frail older people.[23]

Identification of frail older people in primary care

The operationalisation of frailty

To apply a panel management strategy in the care of frail older patients, GPs first must be able to identify frail older people in the population. Currently, although there is consensus on the conceptual definition, no consensus exists on the operationalisation of frailty.[6] Depending on the instrument used, the reported prevalence of frailty varies from 4% to 59%.[24] The prevalence increases with age, and women are more often frail than men. Frailty, disability, and multimorbidity are overlapping but distinct concepts: 4% to 27% of frail older people do not have either multimorbidity or disability.[3,25] Frailty overlaps frequently with disabilities in Instrumental Activities of Daily Living and mobility but less often with disabilities in Basic Activities of Daily Living.[7] Frail older adults use more medication than any other population subgroup, and through falls, confusion, GI blood loss, and other adverse effects, polypharmacy can seriously destabilise the health status of a frail older person.[17]

Regarding the operational definition of frailty, several approaches have emerged from the literature, which could theoretically all be implemented in primary care. The results of the measurements used in these approaches could be registered in general practices' EMRs and, as such, serve as a basis for panel management of frail older people. First, performance-based instruments exist, such as the Frailty Phenotype, which considers frailty to be a syndrome characterised by the following symptoms: unintentional weight loss; self-reported exhaustion; low energy expenditure; low gait speed; and weak grip strength.[26] Individuals with 3-5 factors present are considered frail, individuals with 1-2 factors are considered pre-frail, and individuals without any factors are considered robust. There is on-going discussion regarding the number and nature of items that should be included in the phenotype; it does not readily grade frailty, and as it contains two performance-based items, which require additional time and resources, the Frailty Phenotype is difficult to implement in daily clinical practice.[25,27] Second, questionnaires such as the Tilburg Frailty Indicator (TFI) or Groningen Frailty Indicator (GFI) would be applicable in the frailty screening process, but they do not constitute the optimal first screening step because of their considerable risk of non-response.[28] Third, tools relying on clinical judgement, such as the clinical frailty scale, have been developed.[29] By their nature, just like the performance-based measurements, these tools require the patient to be present to enable an appropriate clinical assessment. Therefore, they are not suitable for frailty identification in a panel management approach, in which patients who do not present for consultations are also taken into consideration.

In a fourth approach, defined by the Frailty Index (FI), frailty is considered a state related to the accumulation of health deficits, such as symptoms, diseases, or impairments.[30] The proportion of deficits of a predefined list present in a patient is the resulting FI score. For example, 20 deficits present out of a list of 60 yields an FI score of 0.33. The FI appears to be a robust measurement: the various FIs reported in the literature, although constructed with different sets and numbers of deficits, have all been strongly correlated with adverse health outcomes.[8,25,27] A drawback of the FI is that information about a broad spectrum of health deficits must be present. However, software-based screening of routine care data could facilitate efficient application of the FI in frailty screening in older people, without the necessity to gather additional data.[27]

Frailty screening in primary care: the use of routine care data

In conclusion, the frailty concept is operationalised in different ways, which can all serve to screen for frailty in older patients in primary care. A Comprehensive Geriatric Assessment (CGA) is seen as the reference standard for detecting frailty, but because of the time and expertise it requires, the CGA cannot be used as a first step to detect frailty in primary care.[25] Instead, a two-step approach should be applied, in which a simple frailty screening tool is used for primary selection of high-risk older people, followed by a detailed tool, such as a CGA, to identify those frail older patients at greatest need for complex care interventions.[12] For initial screening, the use of available routine care data, such as data on medication use, consultation intervals, and FI deficits, in the GP's EMRs seems promising: the EMRs capture the relevant clinical information, no additional data collection is required, and the frailty selection can be performed with a software application embedded in the EMR system, enhancing ease-of-use in daily clinical practice. However, so far, evidence for the effectiveness of EMR-based frailty screening of older people in primary care has been lacking.

Thesis aim

The aims of the studies described in this thesis are to develop and validate U-PRIM, a screening instrument for frailty in community-dwelling older people based on routine primary care data, and to evaluate its effectiveness and cost-effectiveness when screening is embedded in regular GP care (U-PRIM intervention) or when it is followed by a structured nurse-led proactive personalised care program (U-PRIM + U-CARE intervention).

In the first part of this thesis, we present the development and validation of U-PRIM, with a focus on one of its components: the FI. In **chapter 2**, we report the study protocol

of the U-PROFIT trial, in which we describe the U-PRIM instrument. In **chapter 3**, we evaluate the prognostic value of the FI for the prediction of adverse health outcomes. Next, in **chapter 4**, we report on a systematic review of the psychometric properties of the FI. To assess whether the FI identifies the same individuals as frail as the GFI questionnaire, we compare these two measurements in a cross-sectional study in **chapter 5**.

In the second part of this thesis, we evaluate the effectiveness of the U-PRIM frailty-screening instrument and explore how the instrument could be refined. In **chapter 6**, we report on the results of the U-PROFIT clinical trial, and in **chapter 7**, we discuss the results of the cost-effectiveness study that we conducted alongside the U-PROFIT trial. In **chapter 8**, we explore the predictive ability of different versions of the U-PRIM instrument, which we improved based on our experiences, for adverse health outcomes of nursing home admissions and for mortality. These different versions of the U-PRIM instrument could be used in a proactive population care approach or in individual risk assessment of older patients during consultations. Finally, we position our findings in the context of other research, elaborate on methodological challenges, and discuss implications for further research and clinical practice in **chapter 9**, and conclude with a summary of findings in chapter 10.

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Chapter 2

Proactive and integrated primary care for frail older people: design and methodological challenges of the Utrecht Primary care PROactive Frailty Intervention Trial (U-PROFIT)

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Abstract

Background

Currently, primary care for frail older people is reactive, time consuming and does not meet patients' needs. A transition is needed towards proactive and integrated care, so that daily functioning and a good quality of life can be preserved. To work towards these goals, two interventions were developed to enhance the care of frail older patients in general practice: a screening and monitoring intervention using routine healthcare data (U-PRIM) and a nurse-led multidisciplinary intervention program (U-CARE). The U-PROFIT trial was designed to evaluate the effectiveness of these interventions. The aim of this paper is to describe the U-PROFIT trial design and to discuss methodological issues and challenges.

Methods and Design

The effectiveness of U-PRIM and U-CARE is being tested in a three-armed, cluster randomized trial in 58 general practices in the Netherlands, with approximately 5000 elderly individuals expected to participate. The primary outcome is the effect on activities of daily living as measured with the Katz ADL index. Secondary outcomes are quality of life, mortality, nursing home admission, emergency department and out-of-hours General Practice (GP), surgery visits, and caregiver burden.

Discussion

In a large, pragmatic trial conducted in daily clinical practice with frail older patients, several challenges and methodological issues will occur. Recruitment and retention of patients and feasibility of the interventions are important issues. To enable broad generalizability of results, careful choices of the design and outcome measures are required. Taking this into account, the U-PROFIT trial aims to provide robust evidence for a structured and integrated approach to provide care for frail older people in primary care.

Trial registration

NTR2288

Background

With an increasing number of older people in society, the number of frail older people with complex care needs will rise.[1] Frailty is a term often used among health care professionals to characterize older people who have a functional loss of resources in different domains. Frail older people have an increased risk for adverse health outcomes, such as mortality, morbidity and institutionalization.[2-5] The increasing number of frail older people will seriously challenge the health care system because primary care for these patients is currently fragmented, time consuming and reactive.[6] Because the care system does not address their needs, many older patients and their caregivers have a poor quality of life.[7,8] To preserve functional performance and maintain independent living in this vulnerable population, a transition is needed towards more proactive, integrated and structured health care for older people.

Until today, scientific evidence on how primary care providers can provide optimal care for frail older people with complex care needs is inconsistent. Previous intervention studies often used a selection of patients at risk combined with an additional geriatric assessment and follow-up visits.[9,10] However, evidence for these complex interventions is not clear. Moreover, it is unclear what the independent effectiveness of these interventions is.

One widely studied approach to select patients at risk is panel management. Panel management involves periodic reporting of clustered electronic medical record data from a certain 'patient panel' as an overview of the most important health parameters.[11,12] Missed patient encounters and care gaps can then easily be identified, which enables proactive, integrated and timesaving care. Panel management programs have been set up for various chronic diseases; however, integrated panel management approaches for frail older patients are lacking.[13]

Other solutions to prevent functional decline are complex interventions, such as preventive home visiting programs with comprehensive geriatric assessments.[9,14-16] Little is known about the effectiveness of the different interacting components of these complex interventions. Elements that were demonstrated to be promising in different intervention studies are a multidisciplinary, multifactorial approach with tailor-made interventions and an individual assessment for frail older people provided by a (primary) care team with long-term follow-up.[17-19]

To understand the effectiveness of these different approaches, we developed two interventions: a screening and monitoring intervention using routine healthcare data with the Utrecht Periodic Risk Identification and Monitoring system (U-PRIM) and a nurse-led multidisciplinary intervention program, U-CARE. In the **U**trecht **P**rimary care

P**RO**active **F**railty **I**ntervention **T**rial (U-PROFIT), the effectiveness of the U-PRIM intervention, alone and in combination with U-CARE, will be assessed in comparison to usual care. The aim is to preserve physical functioning and improve quality of life for frail older people and their caregivers. The trial will be conducted from October 2010 to spring 2012. The aim of this paper is to describe the design of the U-PROFIT trial, the content of the two interventions and its methodological challenges.

Methods

Design and setting

A single-blind, three-armed, cluster-randomized controlled trial with a one-year follow-up is being conducted (see Figure 1). Recruitment was performed in three primary care networks with almost 70 practices in Utrecht, the Netherlands.

Participants

Inclusion criteria

Selection of patients is performed by the U-PRIM system, a software application that is installed in all participating general practices. Exploring the electronic medical records (EMRs) in each general practice, U-PRIM will screen for three inclusion criteria in patients aged 60 years or older:

- Multimorbidity (defined as a frailty index score of ≥ 0.20; see the 'U-PRIM intervention' section)

  AND / OR

- Polypharmacy (defined as the chronic use of five or more different medications[20])

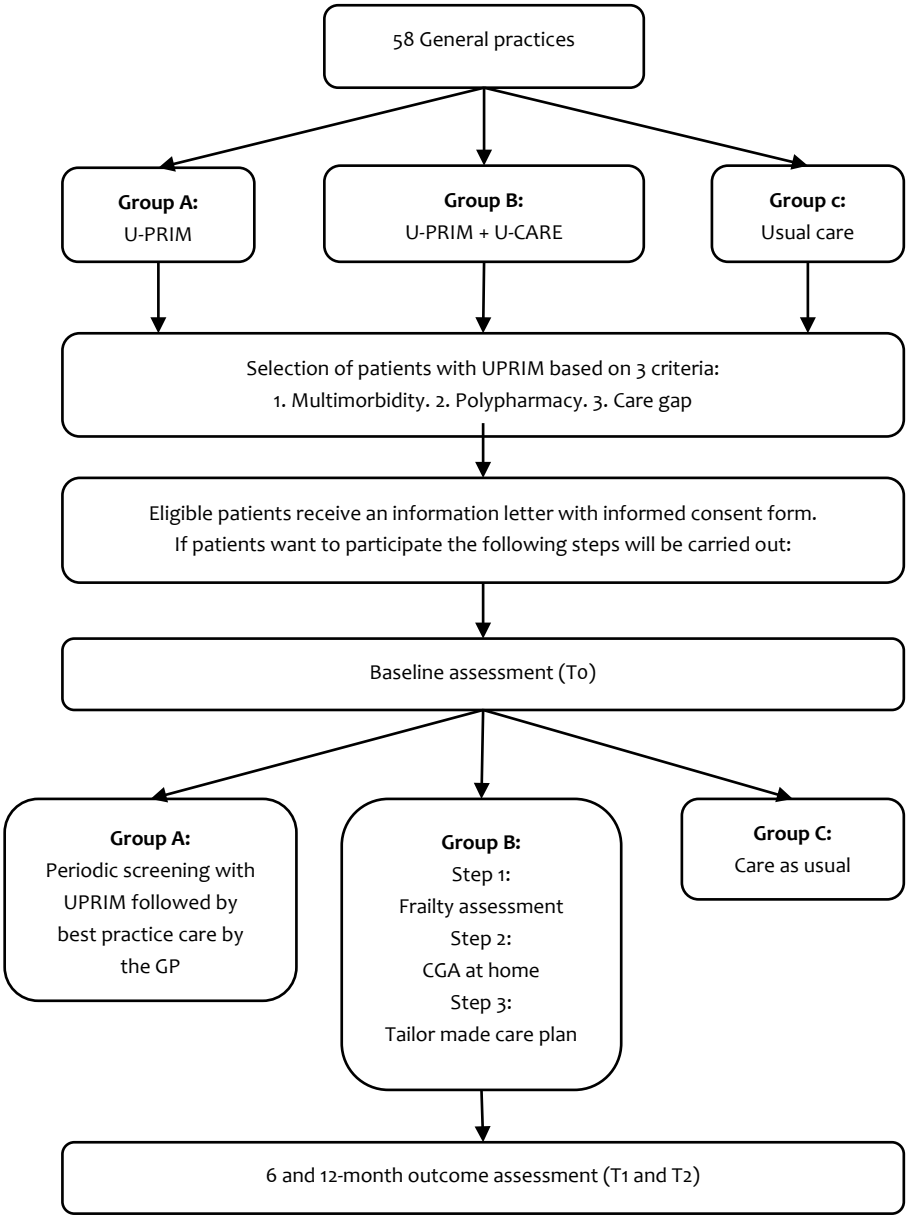
  AND / OR

- Care gap in primary care of three or more years (defined as not having consulted the GP in the past three years, except for the yearly influenza vaccination).

Exclusion criteria

Terminally ill patients or patients living in an elderly home or nursing home are excluded. Reasons for exclusion are registered on the general practice level.

Figure 1. Flowchart



Procedure

At the start of the inclusion period, U-PRIM automatically generates a list of frail patients of 60 years and older in every participating practice. Using the U-PRIM software, data extractions from the electronic medical records (EMRs) in the practices are uploaded to an external server area. Here, reports on frail patients are generated and delivered back to the general practice. To guarantee patient privacy, U-PRIM software encodes the personal data by means of a third trusted party procedure, so personal data are only disclosed to the general practice personnel.

Eligible patients are listed in the first U-PRIM report. These patients are approached by their GP with a patient information letter and informed consent form for participation in the U-PROFIT trial. In addition, patients are asked if they have an informal caregiver. If so, the caregiver is also invited to participate in the study to investigate caregiver burden.

In the practices in the control group, a similar U-PRIM report with potentially frail patients is generated, but this report is not visible to the GP.

Ethical considerations

The U-PROFIT trial is approved by the Institutional Review Board of the University Medical Center Utrecht (UMCU) with protocol ID 10-149/O and registered in the Netherlands Trial Register: NTR2288.

Randomization and blinding

The participating general practices are randomly allocated to one of the two intervention groups (A or B) or the control group (C) by cluster randomization on the general practice level (see flowchart Figure 1). Practices in group A are allocated to the U-PRIM intervention, those in group B to the U-PRIM plus U-CARE intervention and the practices in group C formed the control group. Within the 58 participating general practices, clusters are created because some general practices are working closely together at the same location. Before randomization, clusters are stratified according to the expected number of frail older people in the general practice. The cluster size is estimated based on the number of invitations for the yearly influenza vaccination per practice.

Blinding

Informed consent

A modified informed consent procedure is used to maintain a single-blind design; the so-called "consent to postponed information".[21,22] With this procedure, a valid assessment of subjective outcomes can be obtained in a trial even if the patients cannot be blinded to the intervention. Additionally, selection bias and dropout in the control group can be reduced. In the U-PROFIT trial, patients were not informed as to which intervention group their general practice was allocated until the end of the follow-up period.

Blinding of the GPs and practice nurses

Blinding the GPs and their practice nurses is not possible in this study because they are part of the intervention.

Blinding the investigators

Because the investigators need to directly communicate with the general practices about the study, it is not possible to blind the investigators. However, during data analysis, investigators will be blinded to the data. When the data analysis is completed, this information will be disclosed to the investigators.

The interventions

Two interventions are being tested in the U-PROFIT trial: 1. Screening and Monitoring of frailty (U-PRIM) and 2. Nurse-led multidisciplinary intervention program (U-CARE).

Intervention 1: U-PRIM

The U-PRIM software application is an electronic monitoring system aiming at identification of older patients at increased risk of frailty in routine health care data. The software is based on periodic screening for relevant risk factors in the EMRs of the general practice.

U-PRIM screens for three core risk factors in patients aged 60 years or older. These are also the eligibility criteria of the U-PROFIT trial as described earlier (multimorbidity, polypharmacy and a care gap).

Multimorbidity

The frailty index concept is used as an indicator of multimorbidity.[23] The frailty index uses 50 so-called 'health deficits': symptoms, signs, diseases, social problems and functional impairments, all routinely encoded in the EMR using International

Classification of Primary Care (ICPC) codes (see appendix 1). In the choice of the deficits, we followed previously published guidelines for the construction of a frailty index.[24]
U-PRIM assesses the number of deficits in each individual. The frailty index score expresses the number of deficits present as a proportion of the total number of deficits.[25] Thus, a patent with 15 deficits has a frailty index score of 0.30 (15/50). For this study, multimorbidity based on the frailty index alone is defined as a frailty index score of ≥ 0.20.[26]

Polypharmacy
The U-PRIM software screens the medication list for chronic drug use, using anatomical therapeutic chemical (ATC) codes. Chronic use is present when the medication was prescribed at least three times in the past year, with at least one prescription in the last six months. Polypharmacy is in this study is defined as 5 or more different drugs in chronic use in the past year.[20]

Care gap
The period that patients are out of sight of their GP is assessed to include possible care avoiders prone to self-neglect, for example patients with dementia, psychiatric conditions or alcohol abuse.[27] For this study, a "care gap" is defined as a period of at least 3 years without GP consultation, excluding the annual influenza vaccination.

The U-PRIM procedure
In the U-PROFIT trial, the periodic U-PRIM frailty screening of the trial population takes place every three months in intervention groups A and B. This results in a U-PRIM report for each general practice with a selection of older patients at high risk of adverse health outcomes. Patients are prioritized by means of the frailty index score, with possibilities to prioritize according to polypharmacy or care gap. For an example of a U-PRIM report, see appendix 2.
The report will be passed on to the GP in intervention groups A and B. In group A, GPs are asked to act upon the U-PRIM report in accordance with current available guidelines and best practices and to carry out interventions among the frail elderly patients if needed. In group B, all patients selected by U-PRIM will receive the additional steps of the U-CARE program (see intervention 2). In every participating practice in group A and B, a staff member is responsible for generating the reports with the U-PRIM computer program and for distributing the report among the care providers involved. These contact persons received protocolised, one-on-one guidance with the first U-PRIM

report, with an explanation of the software application and suggestions on how to implement the report in daily clinical practice.

Intervention 2: U-CARE program

U-CARE is a nurse-led, multidisciplinary intervention program to be used in frail patients selected by U-PRIM. Specially trained, registered practice nurses provide structured and integrated care based on a patients' needs approach.

U-CARE is developed by a multidisciplinary team consisting of researchers and practitioners in nursing and primary care medicine. Three experienced practice nurses, a panel of experts and a panel of older people are involved to validate the content.

The program consists of three steps. The first step is a frailty assessment for patients at risk. The second step is a comprehensive geriatric assessment (CGA) at home of frail patients. The third step is a tailor-made care plan with evidence-based interventions developed by the practice nurse. Details of the development and the content of the program are described elsewhere.[28]

Step 1. Frailty assessment

The level of frailty in patients at risk selected by U-PRIM will be further explored with the Groningen Frailty Indicator questionnaire (GFI). The GFI is a 15-item validated questionnaire that assesses frailty from a functional ADL/IADL perspective on four domains: physical, cognitive, social and psychological.[29] Scores on each item are zero or one, and the total score ranges from 0 (not frail) to 15 (severely frail). We chose a score of 4 or higher as the relevant cut-off for the selection of patients that should be visited for a comprehensive geriatric assessment.[30] The GFI has shown high internal consistency and construct validity.[31] This questionnaire will be sent to all patients selected by U-PRIM.

The INTERMED for the Elderly (IM-E) and the Groningen Wellbeing Indicator (GWI) are additional assessments included in U-CARE to enable a multidimensional approach and to measure patients' needs and complexity of care among frail patients on the GFI.[32]

Step 2. Comprehensive Geriatric Assessment at home (CGA)

For those patients identified as being frail, a CGA at home is conducted by a registered practice nurse. During this home visit, the practice nurse focuses on patients' health problems and needs in a structured manner based on the outcome of the frailty assessment. Based on the literature and their prevalence, ten health problems in older patients with additional assessments are included in the CGA (see appendix 3).[33-35]

Step 3. Tailor-made care plan

In collaboration with the GP, the practice nurse will prepare a tailor-made care plan based on the outcome of step 2. This tailor-made care plan consists of interventions derived from evidence-based care plans developed by the research team, practice nurses and experts. For all ten health problems assessed in the CGA, separate evidence-based care plans are developed. The use of the care plan ensures uniformity among practice nurses in tailoring and delivering interventions per health problem. Flowcharts with suggested (nursing) interventions per health problem are developed as a practical tool and will help to guide the practice nurses through a structured process of decision making.

Training program

All practice nurses will receive an extended U-CARE training program that consists of 5 weeks of 4 hours of lessons in class and 4 hours of self-study. During this training program, the included frailty assessments, the content of the CGA and the evidence-based care plans will be discussed. The U-CARE training program is set up in collaboration with the University of Applied Science Utrecht in the Netherlands.

One month prior to the start of the trial, all GPs and registered practice nurses from intervention group are participating in a training session of 4 hours in which the content of U-CARE program is explained and discussed. Additionally, a workshop about collaboration between GP's and practice nurses is set up.

Outcomes and measurements

Primary outcome

The primary outcome of the U-PROFIT trial is the level of Activities of Daily Living (ADL) as measured with the Katz ADL index score.[36] The Katz index measures independence of ADL on six items (bathing, dressing, toileting, transferring, eating and the use of incontinence materials). The score ranges from 0 (total independence) to 6 (total dependence), and it is widely used to assess activities of daily living.[37] Baseline ADL functioning (T0) will be compared with ADL functioning after six months (T1) and one year of follow-up (T2). The questionnaire will be filled in by the patient or a proxy relative.

Secondary outcomes

Secondary outcome parameters will be measured at the same time as the primary outcome parameter (T_0-T_1-T_2). Quality of life will be measured with the RAND-36 and EuroQol (EQ-5D) questionnaires.[38,39] Other secondary outcomes are mortality, number of nursing home admissions, number of emergency department and out-of-hours GP surgery visits, and caregiver burden, measured with Self-Rated Burden (VAS) and Carer-Qol.[40]

Additional data collection

Routine health care data will be extracted from the EMRs of the participating practices. Socio-demographic data, such as age, gender, educational level, ethnicity, marital status and living situation, will be gathered at baseline. General practice characteristics, such as size, percentage of older people, working experiences and geographical location of the general practice, will also be gathered.

Process evaluation

To understand the different components, their interaction and the applicability of the U-CARE program, a feasibility study will be conducted among doctors and practice nurses of intervention group B. Furthermore, interventions delivered by the practice nurse or other health care providers will be registered to gain insight into targeted interventions that are performed by the practice nurses.

The U-PRIM system will be evaluated on psychometric properties, prognostic value for adverse health outcomes and in concordance with the GFI, and the system will be refined following a user demands study.

In addition, qualitative data on patients' satisfaction with the U-CARE program will be qualitatively assessed. In the end, various data will be collected to perform a cost-effectiveness analysis, e.g., data on workload of the GP and practice nurses and time registration.

Sample size calculation

At present, a valid estimation of the variance in the KATZ ADL results within and between general practices cannot be given because these data are not available for Dutch populations. For that reason, a formal power analysis for the cluster-randomized trial is not possible. Therefore, it is also not feasible in this study to take into account a potential cluster effect. In line with Faber et al., we assume that any randomization effect per practice will be absent.[41] Furthermore, we assume that with an expected

number of at least 5000 frail older people included, relevant effects can be found on the outcome between the clusters because the power of a trial increases if the number of clusters, subjects, or repeated measures within a subject increases.

Data analysis

The data will be analyzed using SPSS version 17.0. An 'intention to treat' analysis will be carried out to assess the differences between the intervention groups and the control group regarding ADL functional status. The variations in outcome between the groups will be calculated using mixed linear model analysis. Regression analyses and (co)variation analyses will be carried out when relevant to correct for baseline differences between older people in the three groups. Survival analysis using a Cox regression model with Kaplan-Meier survival curves will be used on mortality and admission into nursing homes. As social economic status (SES), gender, age and education are assumed to be potential effect modifiers, subgroup analysis will be applied where relevant. We will also take the working experience of the participating GPs and practice nurses into account in separate analyses.

Discussion

In this paper, we present the research design and methodology of the U-PROFIT trial. This trial assesses the effectiveness of two interventions: a proactive screening and monitoring system and a nurse-led intervention program. U-PROFIT is unique because of the robust and pragmatic study design directly embedded in primary care practice, which maximizes the generalizability of the results. The integration of the U-PRIM proactive screening tool with the U-CARE nurse-led multidisciplinary intervention program, once proven effective, will provide an innovative, practical panel management approach for frail older people that can be broadly implemented in daily clinical practice. We met several challenges during the design and implementation of the U-PROFIT trial.

Design

As mentioned, the two interventions are tested and embedded in routine clinical practice. Therefore, it's hard to create controlled experimental circumstances. We randomized on a practice level, and some practices may have already use screening lists or structured plans to provide care for older people, while others have not. In addition, in some practices, a practice nurse may have already been part of the practice team. Because all practices can be randomized in one of the intervention groups or in the control group, we consider these differences in elderly care at baseline as normal

variations in clinical practice. In this way, both interventions are compared to the broad range of routine clinical care, enabling generalizability.

We chose a three-armed design for several reasons. First, our baseline assumption is that the U-PRIM screening followed by usual care and the combination of U-PRIM and U-CARE will both give better results than current usual care. Additionally, we hypothesize that both interventions are synergistic and that the effect of U-PRIM and U-CARE is more effective than the U-PRIM intervention alone.[42]

Outcome

The effectiveness of the interventions should be assessed on outcomes that are directly relevant for patients and their caregivers. We decided to take ADL functioning as measured with the Katz ADL index as the primary outcome. ADL functioning is generally reported as the most important parameter in the lives of older people.[43] The Katz ADL index is widely used in studies of prognosis and effects of treatments.[37,44]

Additionally, a broad array of relevant secondary outcomes will be assessed to evaluate both interventions. These will be measured based on a combination of self-report, proxy report and data extraction out of routine healthcare data.

Recruitment and compliance

Proper recruitment of older people for a clinical trial is often considered as complex.[45,46] To improve generalizability, it is important that not only healthy people are included but also less fit older people.[43] For logistical reasons, we opted for a postal approach of eligible patients by the participating GPs. In this approach, we tried to find the optimal balance between extensive information provision, which is strongly advised by the Institutional Medical Ethic Committee, and the need for short and simple information letters in this population. Although patients can contact their GP or the researchers for extra clarification, this postal approach might lead to some response bias with fewer cognitively impaired or frailer patients included than with a personal approach. To limit this problem, patients who do not give consent are approached by telephone two weeks after the information letter is sent, and home visits by a research assistant are offered.

Limiting informative censoring is a second challenge in elderly research. Informative censoring occurs when drop-outs happen for reasons directly related to the primary outcome.[47] In U-PROFIT, this can occur because frailer patients are more likely to die before we can evaluate functional status at the end of follow-up. To limit this problem and assess the extent of it, reasons for withdrawal will be collected, and an intention-to-

treat analysis will be performed. Additionally, various retention strategies will be applied, e.g., home visits; interviews by phone when a postal questionnaire is difficult; small incentives, such as a U-PROFIT pen; and a newsletter to keep patients informed about the project.

Development of the U-PRIM system

The U-PRIM system uses criteria that are known from literature to be linked to frailty, disability and morbidity and that have been selected by a local GP focus group as relevant in daily clinical practice.[2,48,49] Small pilot studies have shown that the current U-PRIM criteria identify a significant number of patients at high risk for frailty. However, the psychometric properties of U-PRIM and exact cut-off values for clinically relevant risk groups still have to be further assessed. The influence of EMR data quality on the U-PRIM output should also be examined.[50]

While preparing for the U-PROFIT trial, major effort was put into building the software, implementing the U-PRIM system and testing it. However, during the trial, technical aspects of the U-PRIM system may need to be adjusted.

This might influence the current system of use and acceptance during the trial. We will assist participating centers by means of manuals, ICT assistance, and proactive contact after report generation to check for any content related questions or user feedback. With updates on the practical implications of ongoing U-PRIM research, we hope to keep all participating primary care providers on board. In this way, the U-PRIM system can be further developed into an easy-to-use frailty screening instrument that contributes to efficient and proactive panel management care. Requiring only sound EMR registration habits and periodic data upload, the U-PRIM system is an ideal candidate for efficient risk stratification of older people in primary care.

Feasibility and adherence

The U-CARE program is a complex, multifactorial intervention with multiple components. In the trial, U-CARE will be provided by over 20 practice nurses and over 100 doctors, and optimal implementation is vital. By means of an extended training program and ongoing education during the trial, we aim for a uniform baseline level of knowledge and skills among the practice nurses. However, motivation for proactive care provision and professional experience with older patients can be different within the group of GPs and practice nurses. These differences reflect daily clinical practice, so general conclusions about the effectiveness can be drawn. However, the effectiveness may differ in relation to characteristics of health care professionals. For that reason, we

will perform subgroup analyses. Finally, this program is based on a proactive care approach. Some patients will appreciate the active interference of care providers, but other patients might not and consider it as patronizing. Possible benefits of a proactive outreach should therefore clearly outweigh the unwanted burden it may put on others.

Strengths

Despite many challenges, we think that U-PROFIT offers many opportunities. First, the design of a three-armed, cluster randomized trial enables us to investigate the effectiveness of both interventions separately as well as in combination. Secondly, current literature recommends that trials on frailty should target persons aged 70 and older, because in younger age groups, frailty prevalence is thought to be too low.[3] However, during the development of U-PROFIT, general practitioners suggested to lower the age threshold for inclusion to 60. A substantial part of the ageing population in the practices consists of first generation immigrants of non-Dutch origin. In these elderly individuals, who often came to Holland for physical labor, frailty is reported to appear at a relatively young age.[7] With the inclusion of patients aged 60 years and older in our study, we include the group most relevant in current clinical practice. The frailty index score is demonstrated to be a valuable indicator of the 'frailty state' of an individual. Frailty indices constructed differently, with different deficit content and considering different numbers of deficits, yield closely related results.[25] In this trial, we aim to demonstrate that the frailty index can be used for structured risk assessment in primary care practice, using routine care data. For optimal implementation of the U-CARE intervention, we will maintain a training and supervision process of the practice nurses during the trial. In monthly meetings, special attention will be paid to collaboration between nurses and GPs to achieve optimal functioning of this important team. In addition, lectures and education about geriatric health problems will be performed. During regular project meetings, research updates will be provided to inform nurses and GPs. While the intervention in non-pharmacological intervention studies is often poorly described, the interventions in the U-PROFIT trial consist of well-defined and thoroughly designed components. This will safeguard the reproducibility of the intervention program once the effectiveness is established. Although various challenges have to be addressed, the U-PROFIT trial offers excellent opportunities for a valid scientific evaluation of a structured and integrated approach to improve physical functioning in frail older people in primary care. Once proven effective, it can be broadly implemented in daily clinical practice.

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Appendix 1. ICPC encoded Frailty Index deficits

Deficit	ICPC[a]	ICPC-Label	Days[b]
1	K78	Atrial fibrillation/flutter	365
2	P74	Anxiety disorder/anxiety state	365
3	R96	Asthma	-
4	K77	Heart failure	-
5	T90	Diabetes mellitus	-
6	N88	Epilepsy	-
7	S70	Herpes zoster	365
8	S97	Chronic ulcer skin	365
9	D94	Chronic enteritis/ulcerative colitis	-
10	N89	Migraine	365
11	U99	Urinary disease, other	-
12	K88	Postural hypotension	365
13	L95	Osteoporosis	-
14	R81	Pneumonia	365
15	S91	Psoriasis	-
16	L88	Rheumatoid arthritis / related condition	-
17	P17	Tobacco abuse	-
18	P06	Sleep disturbance	365
19	N87	Parkinsonism, Parkinson's disease	-
20	P15	Chronic alcohol abuse	-
	P16	Acute alcohol abuse	365
21	A01	Pain general/multiple sites	365
	A04	Weakness/tiredness general	365
	A05	General deterioration	365
	P78	Neuraesthenia/surmenage	365
22	B80	Iron deficiency anaemia	365
	B81	Anaemia, Vitamin B12/folate def.	365
	B82	Anaemia other/unspecified	365
23	L89	Osteoarthrosis of hip	-
	L90	Osteoarthrosis of knee	-
	L91	Osteoarthrosis other / related condition	-
24	P20	Memory / concentration / orientation disturbance	365
	P70	Dementia / Alzheimer's disease	-
	P85	Mental retardation	-
25	R91	Chronic bronchitis / bronchiectasis	-
	R95	Chronic obstructive pulmonary disease	-
26	K89	Transient cerebral ischaemia	365
	K90	Stroke/cerebrovascular accident	-

Deficit	ICPC[a]	ICPC-Label	Days[b]
27	P03	Feeling depressed	365
	P76	Depressive disorder	365
28	K02	Pressure/tightness of heart	365
	R02	Shortness of breath/dyspnoea w/o K02	365
29	N17	Vertigo/dizziness	365
	H82	Vertiginous syndrome / labyrinthitis	365
30	L72	Fracture: radius/ulna	365
	L73	Fracture: tibia/fibula	365
	L74	Fracture: hand/foot bone	365
	L75	Fracture: femur	365
	L76	Fracture: other	365
31	H84	Presbyacusis	-
	H85	Acoustic trauma	-
	H86	Deafness	-
32	T05	Feeding problem of adult	365
	T07	Weight gain	365
	T08	Weight loss	365
	T82	Obesity	-
	T83	Overweight	-
33	K86	Hypertension uncomplicated	365
	K87	Hypertension complicated	-
34	K74	Angina pectoris	365
	K75	Acute myocardial infarction	365
	K76	Other / chronic ischaemic heart disease	-
35	D17	Incontinence of bowel	-
	U04	Incontinence urine	-
36	D72	Viral hepatitis	-
	D97	Cirrhosis / liver disease NOS	-
37	A79	Malignancy NOS	
	B72	Hodgkin's disease	-
	B73	Leukaemia	-
	B74	Malignant neoplasm blood other	-
	D74	Malignant neoplasm stomach	-
	D75	Malignant neoplasm colon/rectum	-
	D76	Malignant neoplasm pancreas	-
	D77	Malig. neoplasm digest other/NOS	-
	F74	Neoplasm of eye/adnexa	-
	H75	Neoplasm of ear	-
	K72	Neoplasm cardiovascular	-
	L71	Malignant neoplasm musculoskeletal	-
	N74	Malignant neoplasm nervous system	-

Deficit	ICPC[a]	ICPC-Label	Days[b]
	R84	Malignant neoplasm bronchus/lung	-
	S77	Malignant neoplasm of skin	-
	T71	Malignant neoplasm thyroid	-
	U75	Malignant neoplasm of kidney	-
	U76	Malignant neoplasm of bladder	-
	U77	Malignant neoplasm urinary other	-
	X75	Malignant neoplasm cervix	-
	X76	Malignant neoplasm breast female	-
	X77	Malignant neoplasm genital other (f)	-
	Y77	Malignant neoplasm prostate	-
	Y78	Malignant neoplasm male genital / mammae	-
38	P18	Medication abuse	365
	P19	Drug abuse	365
39	N86	Multiple sclerosis	-
	N94	Peripheral neuritis/neuropathy	-
	N99	Neurological disease, other	-
40	F83	Retinopathy	-
	F84	Macular degeneration	-
	F92	Cataract	-
	F93	Glaucoma	-
	F94	Blindness	-
41	P71	Organic psychosis other	365
	P72	Schizophrenia	-
	P73	Affective psychosis	365
42	K91	Atherosclerosis	-
	K92	other PVD	-
	K99	Cardiovascular disease other	-
43	T85	Hyperthyroidism/thyrotoxicosis	365
	T86	Hypothyroidism/myxoedema	365
44	X87	Uterovaginal prolapse	-
	Y85	Benign prostatic hypertrophy	-
45	K93	Pulmonary embolism	365
	K94	Phlebitis/thrombophlebitis	365
46	D84	Oesophagus disease	365
	D85	Duodenal ulcer	365
	D86	Peptic ulcer other	365
47	A06	Fainting/syncope	365
	A80	Trauma/injury NOS	365
48	A28	Limited function/disability NOS	-
	B28	Limited function/disability	-
	D28	Limited function/disability (d)	-

Deficit	ICPC[a]	ICPC-Label	Days[b]
	F28	Limited function/disability (f)	-
	H28	Limited function/disability ear	-
	K28	Limited function/disability (k)	-
	L28	Limited function/disability (l)	-
	N28	Limited function/disability (n)	-
	P28	Limited function/disability (p)	-
	R28	Limited function/disability (r)	-
	S28	Limited function/disability (s)	-
	T28	Limited function/disability (t)	-
	U28	Limited function/disability urinary	-
	X28	Limited function/disability (x)	-
	Y28	Limited function/disability (y)	-
	Z28	Limited function/disability (z)	-
49	Z12	Relationship problem with partner	365
	Z14	Partner illness problem	365
	Z15	Loss/death of partner problem	-
50	Z01	Poverty/financial problem	365
	Z03	Housing/neighbourhood problem	365
	Z04	Social cultural problem	365
	Z29	Social problem NOS	365

[a] Dutch ICPC-1 version as currently in use in general practices

[b] '365 days' indicates that the belonging ICPC code is only considered present when registered at least once in the past year. For ICPC codes without the '365 days' indication, all time presence is considered.

Appendix 2. Lay-out of U-PRIM report

Patient	Sex	Age	FI score	Multimorbidity	Polypharmacy	Care gap
Smith	F	87	0,26	13	12	5
Jones	M	63	0,22	11	16	18
Taylor	F	70	0,20	11	8	3
Brown	F	75	0,20	10	10	77
Smith	M	81	0,16	8	5	330
Johnson	F	72	0,14	7	6	32
White	F	94	0,08	5	4	1503

Appendix 3. Overview of health problems, assessments, and summary of interventions

Health Problem	Assessment	Interventions and recommendations (summary)	Level of evidence[a]
1. Falls & Mobility	Get-up and Go-test Falls Efficacy Scale (FES-NL)	- Multidisciplinary, multifactorial, health/environmental risk factor; Screening/intervention programs in the community;	- A1
		- A program of muscle strengthening and balance retraining, individually prescribed at home by a trained health professional;	- A1
		- Medication control and, if possible, withdrawal of psychotropic medication.	- A1
2. Physical functioning	Instrumental Activities of Daily Living (IADL scale Lawton & Brody)	- Exercise programs that consist of muscle strengthening, balance retraining, endurance and flexibility;	- A1
		- Motivation, feedback, patient education;	- A1
		- Practice should reflect the opportunities that are available in the community.	-B
3. Nutrition & Malnutrition	Short Nutritional Assessment Questionnaire (SNAQ-65) Mini Nutritional Assessment (MNA)	- Screening the nutritional status	- A1
		- Systematic identification of nutrition problem	- A1
		- Educating health care workers on the consequences of malnutrition	- A1
4. Cognitive decline	Mini Mental State Examination (MMSE) Clock Drawing	- Support, motivating activities of social interaction, cognitive and physical activities	- B
		- Individual programs focus on IADL problems	- B
		- Cognitive stimulation and training	- A1
5. Polypharmacy	Medication review assessment	- Multifactorial interventions are more effective that mono-interventions	- A1
		- Tailored patient education, instruction, support, feedback and follow-up	- A1
		- Tools and reminders for adherence	- A1

Health Problem	Assessment	Interventions and recommendations (summary)	Level of evidence[a]
6. Mood & depression	Mini Mental State Examination (MMSE) Geriatric Depression Scale (GDS) Observation List early symptoms Dementia (OLD) Clock Drawing test	- Screening instruments as part of the intervention strategy - Exercise interventions - Collaboration with other disciplines is essential	- A1 - C - A1
7. Loneliness	De Jong-Gierveld loneliness scale	- Adapted interventions to target patients - Patient education, instruction, referral - Knowledge of health care workers about referral possibilities	- A1 - A1 - C
8. Vision problems & hearing loss	Hearing Handicap Inventory for the Elderly-Screening (HHIE-S)	- Determine the cause of reduced vision - General practitioners have important role in screening (vision) - Knowledge about referral possibilities and environmental adaptations	- A1 - A1 - D
9. Urinary incontinence	Protection Amount Frequency, Adjustment, Body image (PRAFAB)	- Bladder training - Pelvic floor muscles training - Planned bladder	- A1 - A1 - A1
10. Caregiver burden	Experienced burden informal care (EDIZ) Caregiver Strain Index (CSI)	- Ask for use of support. If rejected, ask for underlying reason - Nurses can play an important role in case finding - Multidimensional programs on physical and mental support	- D - C - A2

Legend: [a] Level of evidence: A1: Systematic review of at least two independently conducted studies of A2 level. A2: Well-designed, double blind, randomized controlled trial. B: Comparative studies not randomized but well-designed cohort or case/control analytic studies (preferably from more than one center or research group). C: Observational studies, case series studies. D: Expert opinion.

Chapter 3

Prediction of adverse health outcomes in older people using a Frailty Index based on routine primary care data

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Abstract

Background

A general frailty indicator could guide general practitioners (GPs) in directing their care efforts to the patients at highest risk. We investigated if a Frailty Index (FI) based on the routine health care data of GPs can predict the risk of adverse health outcomes in community-dwelling older people.

Methods

This was a retrospective cohort study with a 2-year follow-up period among all patients in an urban primary care center aged 60 and older: 1,679 patients (987 women [59%], median age, 73 years [interquartile range, 65–81]). For each patient, a baseline FI score was computed as the number of health deficits present divided by the total number of 36 deficits on the FI. Adverse health outcomes were defined as the first registered event of an emergency department (ED) or after-hours GP visit, nursing home admission, or death.

Results

In total, 508 outcome events occurred within the sample population. Kaplan–Meier survival curves were constructed according to FI tertiles. The tertiles were able to discriminate between patients with low, intermediate, and high risk for adverse health outcomes (p value < .001). With adjustments for age, consultation gap, and sex, a one deficit increase in the FI score was associated with an increased hazard for adverse health outcomes (hazard ratio, 1.166; 95% confidence interval [CI] 1.129–1.210) and a moderate predictive ability for adverse health outcomes (c-statistic, 0.702; 95% CI 0.680–0.724).

Conclusions

An FI based on International Classification of Primary Care (ICPC)-encoded routine health care data does predict the risk of adverse health outcomes in the elderly population.

Background

The rising number of frail older people is a major challenge for primary health care.[1] The present reactive approach leads to unplanned presentation of older patients with complex problems, which may increase unnecessary disease burden and the workload for primary care providers.[2] Also, emergency hospitalizations may increase, which in turn threaten functional independence.[3] A shift toward more proactive, population-based care is therefore essential.[4-6] A general frailty indicator that stratifies older patients based on their overall risk of adverse health outcomes could guide general practitioners (GPs) in directing their care efforts to the patients at highest risk. A broad spectrum of frailty operationalisations could serve as such a general frailty indicator, for example, self-report questionnaires such as the Groningen Frailty Indicator, the phenotypic Fried criteria, the Frailty Index (FI), or tools that rely on clinicians' judgment such as the Clinical Frailty Scale.[7,8] Most available measures see frailty as a multidimensional construct varying from only considering multiple physiological domains to also including functional, social, and psychological domains.[9-11] Among these tools, the FI is unique, in that it may easily identify frailty using routine available data out of the GPs electronic medical records (EMR).[12] Therefore, the FI score could be a suitable frailty indicator to facilitate proactive primary care. An FI screen for a predefined list of relevant "health deficits" include diseases, signs, symptoms, and psychosocial or functional impairments. The proportion of deficits present in an individual is the resulting FI score. Theoretically ranging from zero to one, it is a dynamic variable that reflects a patient's overall health status.[13] With proper deficit selection, different FIs applied in community-dwelling older populations showed consistent abilities to determine frailty levels. This is reflected by their abilities to predict various adverse health outcomes, for example, mortality and institutionalization, and by their concordance with other frailty measures, for example, the phenotypic Fried criteria.[14-17] However, none of the published FIs have been derived from and used in routinely collected primary care data.[18] Thus, it is unclear if the performance and validity of the FI can be generalized to this health care setting. Therefore, we examined prediction of adverse health outcomes with an FI based on the routine health care data of GPs.

Methods

Design

A retrospective cohort study among community-dwelling people aged 60 and older in a primary care with a 2-year follow-up period.

Setting

Patients were enrolled from an urban primary health care center with seven GPs caring for 10,500 people in the city of Utrecht, the Netherlands. In the Netherlands, all GPs use an EMR system. In the participating center, "Promedico ASP" is used.[19] Each patient contact is encoded using International Classification of Primary Care (ICPC) codes.[20] Prescriptions are automatically encoded with Anatomical Therapeutic Chemical codes.[21]

Procedures

In the center, frailty screening software was installed.[22] When applied to EMR data, this program calculates the frailty levels of elderly patients using an FI with ICPC-coded deficits and an additional polypharmacy deficit. The software also reports on consultation gaps, age, and sex. A consultation gap is a time frame in which patients do not have any contact with the primary care center, with the exception of the yearly influenza vaccination. In practice, the frailty screening software uploads EMR data to a highly secured server area where frailty reports are generated and then sent back to the primary care center. During this process, encoded personal data are pseudonymised by a trusted third party, resulting in completely anonymous data processing and analysis outside the general practice.[23]

Participants

Participants were selected using an EMR data file containing patient information up to November 10, 2010. In this anonymous data set, November 10, 2008 was considered as the baseline date, with patients aged 60 and older at baseline eligible for inclusion. We excluded patients who had been transferred to other primary care centers but whose records were still contained in the baseline data set of this center due to administrative delay. For the included patients, the frailty screening software determined the baseline FI scores, consultation gaps, age, and sex as baseline covariates. Next, EMR follow-up data were screened for emergency department (ED) or after-hours GP surgery visits, nursing home admission, or death as adverse health outcomes.

Baseline Measurements

Frailty Index

We first selected 140 relevant ICPC-coded items and a polypharmacy item. This selection was based on the literature on FI construction, data on age-related deficit prevalence and health burdens, and a consensus meeting with a local expert group of GPs.[24,25] Second, we arranged these items into single- and multi-item deficits so that each deficit had a prevalence of at least 5%, and multi-item deficits reflected a clinically relevant combination of ICPC-coded items. For example, none of the ICPC-items such as retinopathy, blindness, and macular degeneration reached 5% prevalence, so we combined these items together with glaucoma in a single "visual impairment" deficit. The total selection and arrangement procedure resulted in an FI with 36 deficits (see Supplementary Table 1). In the baseline EMR data, the frailty software screened all patients for deficits. For some deficits, for example, diabetes, all available data for each patient were screened. For others, for example, depression, only data from the past year were considered. This strategy enables deficits to transition from "present" to "absent" in follow-up FI assessments, so that improvement of the FI score becomes possible over time. To calculate the polypharmacy deficit, defined as at least five different chronically prescribed medications, the frailty software screened for Anatomical Therapeutic Chemical codes. Medication which was prescribed three times in the past year with at least one prescription in the last 6 months was considered as medication in chronic use. An ICPC-encoded deficit was present when at least one-related ICPC code was registered. For single-item deficits such as "heart failure," this implied a positive ICPC-encoded item "K77—heart failure." For multi-item deficits such as "hearing impairment," one or more of the three-related ICPC-encoded items (H84—presbycusis, H85—acoustic trauma, or H86—deafness) were required to be positive. The FI score was defined as the proportion of deficits present. For example, 12 deficits out of 36 provided a FI score of 0.33.

Consultation gap

We considered the number of days since a patient's last phone contact or visit with a GP as an overall consultation gap. The frailty software determined this time frame by screening for the date of the most recently registered ICPC code with the exception of influenza vaccination.

Outcome Measures

ED and after-hours GP surgery visits

The frailty software screened the EMR data file for ED and after-hours GP surgery consultations that occurred during the follow-up period (query syntax available upon request). The date of the patient's first visit was chosen as the date of outcome occurrence.

Mortality and nursing home admission

Patient data from those who had left the practice population during the follow-up period were screened for death and nursing home admissions. In the EMR data file, the frailty software searched for ICPC code A96 (death) and for characteristics and key words related to death or nursing home admission up to 4 weeks prior to the departure date (query syntax available upon request). We chose the departure date from the primary care center as the date of outcome occurrence. Only long-term care nursing home admissions were taken into consideration. Short-term care nursing home admissions would be captured by preceding ED and after-hours GP surgery visits.

We combined all abovementioned outcome measures in one single adverse health outcome measure. Therefore, only patients' first registered adverse event was considered as an outcome in the analysis. The follow-up period was calculated as the number of days from November 10, 2008 until the event date. For patients without events, the follow-up period was calculated from November 10, 2008 until the end of the study or until the patient's departure from the center for reasons other than those assessed here. The automated frailty screening for the occurrence of adverse health outcomes was twice verified by the first and last author using anonymous patient data.

Statistical Methods

First, descriptive statistics were calculated for the baseline characteristics according to data for the overall population as well as for the patients grouped according to FI tertiles. Second, the distribution of the FI score and its relation to patient age were plotted. Survival curves were then constructed to evaluate event-free survival probabilities per FI tertile. Differences were tested with the log rank test. Next, univariable models were constructed for the FI and other baseline variables in relation to the hazards of adverse outcomes, with c-statistics calculated to assess their discriminatory ability. Multivariable Cox regression analyses were performed to assess the independent predictive capacity of the FI and to evaluate the discriminatory ability with other baseline variables added to the model. We studied the hazard ratios per

deficit increase in the FI. The proportional hazards assumption was assessed with the scaled Schoenfeld residuals test.[26] Using simple bootstrap resampling with a *B* of 200, 95% bias-corrected accelerated confidence intervals (CIs) were constructed.[27] In all hypothesis tests, *p* values less than .05 were considered statistically significant. Analyses were performed using PASW version 18 (SPSS, Chicago, IL) and R (R Foundation for Statistical Computing, Vienna, Austria).

Ethics

This study is part of the U-PROFIT trial, which has been approved by the Institutional Review Board of the University Medical Center Utrecht (reference: 10–149/O).[22] This substudy solely encompasses anonymous EMR data research, and therefore separate permission was not necessary.

Results

In the baseline EMR data, we identified 1,685 eligible patients of whom 6 were excluded because they had already left the primary care center before baseline. For the 1,679 included patients, all baseline variables and outcome measures could be calculated. Patients in higher FI groups were older, more often women, and had shorter consultation gaps than patients in the lowest FI group (Table 1).

Table 1. Baseline characteristics of the total study population and of patients grouped per Frailty Index score tertile

Variable	Total study population n = 1679	FI tertile 1 (0.00 – 0.03) n = 497	FI tertile 2 (0.04 – 0.13) n = 643	FI tertile 3 (≥ 0.14) n = 539	Significance p-value
Women, n (%)	987 (58.8)	261 (52.5)	371 (57.7)	355 (65.9)	< .001[a]
Age, median (IQR)	73 (65 - 81)	65 (62 - 73)	72 (65 - 79)	80 (73 - 86)	< .001[b]
FI score, median (IQR)	0.08 (0.03 - 0.14)	0.03 (0.00 - 0.03)	0.08 (0.06 - 0.11)	0.17 (0.14 - 0.22)	< .001[b]
Consultation gap in days, median (IQR)	27 (11 - 98)	110 (25 - 283)	28 (12 - 77)	14 (6 - 28)	< .001[b]

[a] Difference between FI tertile groups evaluated with Pearson Chi-Square. [b] Differences between FI tertile groups evaluated with Kruskal-Wallis test. FI = Frailty Index, IQR = interquartile range

The median FI score was 0.08 (interquartile range, 0.03–0.14) for women and 0.06 (interquartile range, 0.03–0.14) for men (*p* value, <.001). The FI had a right-skewed distribution with an upper 99% limit of 0.31, range 0.00–0.42 (Figure 1A). The mean FI according to age increased steadily with +0.004 per year on a linear scale (Figure 1B), with no relevant difference between men (+0.004; 95% CI, +0.003 to +0.005) and women (+0.003; 95% CI, +0.003 to +0.004).

Figure 1. Frailty Index Score Distribution and Mean Frailty Index Score per Age Group

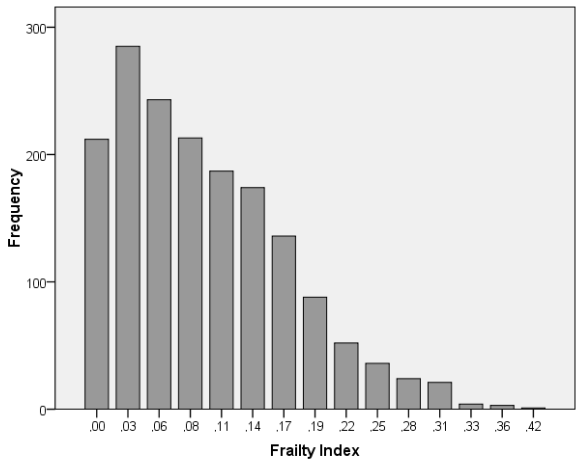


Figure 1A. Distribution of the Frailty Index.

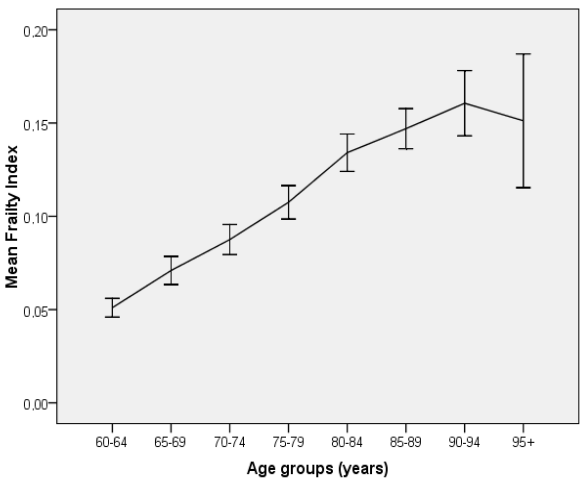
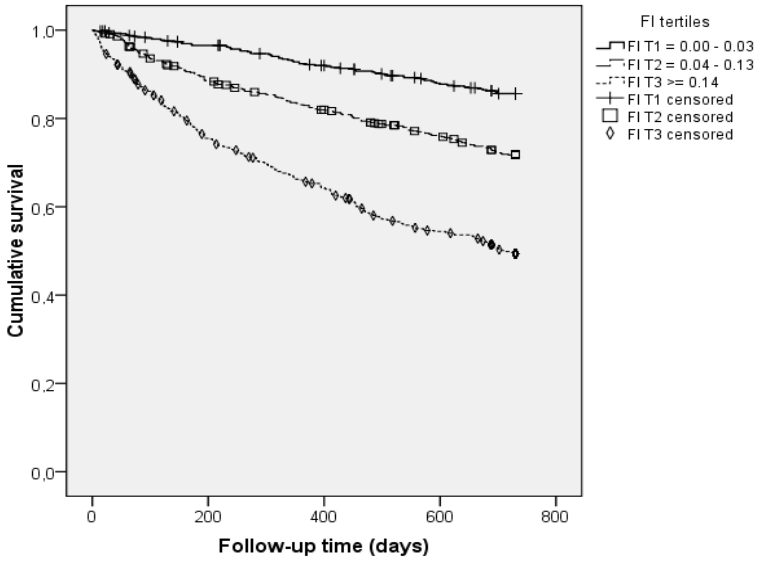


Figure 1B. Mean Frailty Index according to age group.
Bars represent 95% confidence intervals around the mean.

The following five deficits were most prevalent: uncomplicated hypertension (35.8%), polypharmacy (28.8%), diabetes mellitus (18.8), cataract (13.4%), and sleep disturbance (11.5%). Survival analysis confirmed that the FI scores could be used to determine patient risk for adverse health outcomes (Figure 2, *p* value < .001).

Figure 2. Kaplan-Meier event-free survival curves per Frailty Index score tertile



Log rank test: Chi-Square 175.174, df 2, p-value < 0.001

In total, 508 patients (30%) experienced an adverse outcome event during the follow-up period. A positive relationship between the FI scores and the number of adverse health outcomes was observed (Table 2). In the univariable Cox regression analysis, the FI predicted hazards for adverse health outcomes (Table 3; hazard ratio, 1.246; 95% CI, 1.217–1.283). The scaled Schoenfeld residuals were not associated with time (data available on request). The FI had the highest discriminative ability for adverse health outcomes in comparison with age, consultation gap, and sex. (c-statistic, 0.686; 95% CI, 0.664–0.708). Although adjustment for age partly explained the predictive capacity of the FI, it still remained a predictive factor for adverse health outcomes (Table 3; hazard ratio, 1.184; 95% CI, 1.153–1.224). Adding age as a covariate along with the FI improved the predictive ability (c-statistic, 0.701; 95% CI, 0.679–0.723). Discrimination between high- and low-risk groups for adverse events did not improve when adding sex and consultation gaps as covariates.

Table 2. Mean follow-up time, nature of first adverse health outcome and reasons for censoring of the total study population and of patients grouped per Frailty Index score tertile

Variable	Total study population n = 1679	FI tertile 1 (0.00 – 0.03) n = 497	FI tertile 2 (0.04 – 0.13) n = 643	FI tertile 3 (≥ 0.14) n = 539	Significance p-value
Follow-up time, (days), mean (SD)	574 (244)	655 (177)	595 (230)	473 (277)	< .001[a]
First event, n (% of total population or FI tertile)					
Mortality	41 (2.4)	9 (1.8)	14 (2.2)	18 (3.3)	.241[b]
Nursing home	21 (1.3)	2 (0.4)	6 (0.9)	13 (2.4)	.010[b]
≥ 1 ED or out-of-hours GP surgery visits	446 (26.6)	58 (11.7)	157 (24.4)	231 (42.9)	< .001[b]
Reasons for censoring before end of study, n (% of total population or FI tertile)					
Moving out of area	72 (4.3)	19 (3.8)	22 (3.4)	31 (5.8)	.119[b]
Moving to assisted living facility	26 (1.5)	2 (0.4)	5 (0.8)	19 (3.5)	< .001[b]
Unknown	78 (4.6)	15 (3.0)	18 (2.8)	45 (8.3)	< .001[b]

[a] Difference between FI tertile groups evaluated with ANOVA. [b] Difference between FI tertile groups evaluated with the Pearson Chi-Square test. ED = emergency department, FI = Frailty Index, GP = general practitioner, SD = standard deviation

Table 3. Crude and adjusted predictive capacity of the Frailty Index for ED / Out-of-hours GP surgery visits, nursing home admission, and mortality as combined adverse health outcomes

	Hazard Ratio	95 % CI	*P* value	C-statistic	95% CI
Univariable analysis					
FI	1.246	1.217-1.283	.005	0.686	0.664-0.708
Age	1.060	1.050-1.068	.005	0.655	0.631–0.678
Consultation gap	0.900	0.861-0.935	.005	0.622	0.598–0.646
Sex	1.146	0.928-1.374	.174	0.517	0.495–0.538
Multivariable analysis I (with below-mentioned combination of independent variables)					
FI	1.184	1.153-1.224	.005	0.701	0.679-0.723
Age	1.037	1.024-1.048	.005		
Multivariable analysis II (with below-mentioned combination of independent variables)					
FI	1.166	1.129-1.210	.005	0.702	0.680-0.724
Age	1.036	1.025-1.046	.005		
Consultation gap	0.964	0.937-0.986	0.025		
Sex	0.941	0.796-1.105	0.483		

Effects are depicted per deficit increase in the FI, per year increase in age, per adjacent medicine in chronic use and per month increase in consultation gap. Male sex was taken as the reference value. CI = confidence interval, ED = Emergency Department, FI = Frailty Index, GP = General Practitioner. 95% Bias corrected accelerated confidence intervals are constructed with simple sampling bootstraps, B=200.

Discussion

We demonstrated that an FI based on ICPC-coded routine health care data can adequately predict adverse outcomes in community-dwelling older patients. The risk of adverse outcomes, such as mortality and institutionalization, is widely considered as a proxy measure for frailty.[17,28-30] Using this proxy measure, we demonstrated that the capacity of the FI to determine frailty levels can be generalized to the primary care setting. This provides an opportunity for application of the FI as a risk stratification tool in daily primary care practice.

One strength of our study is that we were able to analyze data from older patients of a large primary health care center without having the risk of selection bias, thus enabling broad generalizability to the community-dwelling older population. Furthermore, the outcomes we assessed represent the clinically relevant derailment of patients.

Our analyses have some limitations. First, the risk of missing data caused by informative censoring should be considered. Informative censoring occurs when patients lost during follow-up have a different outcome risk than do the patients who completed the study.[31] For example, 20 of the 26 patients who were lost during the follow-up period due to moving to an assisted living facility had high FI scores (Table 2). These patients probably had a relatively high risk of adverse health outcomes, and not considering these events in our analysis could lead to an underestimation of the predictive value of the FI. However, considering the small number of patients concerned, the influence on our study results will be limited. Second, there is no consensus on whether different adverse health outcomes should be combined in one outcome measure. We opted for this approach because we aimed to construct a general, easy-to-use risk score. Care providers prefer an overall risk estimate, and both ED and after-hours GP surgery visits can represent an initial sign of general derailment eventually leading to nursing home admission or death. One might argue that after-hours GP surgery visits could just as well reflect scheduling problems during regular primary care hours. This, however, seems improbable because in the Netherlands, triage nurses function as gatekeepers for GPs after-hours care, only allowing patients with urgent care demands access to this service.[32] Moving to an assisted living facility was not included as an adverse health outcome, as the support offered by assisted living could also be seen as a positive, planned intervention to maintain a high level of independency as long as possible. The FI should also be able to predict the risk of solely death and nursing home admission as a combined outcome measure. Indeed, after adjustment for age, consultation gap, and sex, the FI predicted the combined adverse event of nursing home admission and death and showed good discriminative accuracy (hazard ratio, 1.126; 95% CI, 1.061–1.190; c-

statistic, 0.797; 95% CI, 0.764–0.830). This discriminative accuracy seems comparable with the AUCs reported for 1-year mortality of four different frailty instruments applied in a hospitalized population.[33]

Several other studies mentioned their FI to be based on clinical data that can be routinely collected.[14,34-36] Data in these studies, however, were especially collected for the study itself, resulting in enhanced data completeness. Using administrative routine health care data, we showed in our study that the generalization of the predictive value of the FI to a general practice setting is indeed possible. Nevertheless, our FI showed a surprisingly narrow score range, with an upper 99% limit of 0.31 as compared with ~0.60 in other studies. This difference might exist for several reasons. First, we hypothesized that this might be related to our relatively low age limit for inclusion of patients aged 60 and older. However, repeating the analyses including only patients aged 70 resulted in the same deficit accumulation rate and 99% upper limit (data available upon request). The scale differences might be related to the nature of this FI, with deficits being extracted from routine health care data. First, patients might not contact their GP about every "deficit" they have. Second, GPs might not properly encode every symptom or diagnosis in the EMR data. For example, the baseline prevalences of the "limited function or disability" ICPC-items (all items <1%) as reported in Supplementary Table 1 likely reflect major underreporting, since about 20% to 30% of community-dwelling people older than 70 years are known to have some degree of disability in mobility or (instrumental) activities of daily living.[38,39] Third, we considered some deficits as present only when they are registered at least once in the past year, and finally, the scaling differences might also be related to fine tuning of the frailty software system. Usually, a prevalence of 1%–2% is considered sufficient for an item to be included in an FI. We, however, included only deficits with a prevalence of at least 5%, to keep our FI score range as broad as possible. This might indicate that when using routine care data as the information source, different criteria for deficit selection are needed. Furthermore, the clinical relevance of the FI should be carefully weighed against that of possible other "frailty state variables" that can easily be extracted from EMR data. When considering the c-statistics, adding age as covariate along with the FI resulted in an increased predictive ability. However, with a correlation coefficient between age and the FI of 0.476, the FI seems to add sufficient additional information to justify further exploration of this concept. These results are in line with previous studies that indicate the adjacent value of the FI to chronological age.[39,40] However, albeit with scores on a much narrower range than usual, our FI, with a deficit list similar but not equal to previous FIs, does predict adverse health outcomes in primary care. It also shows a similar

right-skewed distribution with women and older patients having higher FI scores. All of these features support the validity of our FI, and the robustness of the FI concept in general, in which not the nature of health problems but rather the number of problems each patient has appears to be essential.[41] In conclusion, our results support the notion that an FI could be used as a frailty screening tool, after which integrative and multidisciplinary patient management that meets the needs of frail older patients should follow.[42-44] Also, summarizing routine health care data in an easy interpretable score such as the FI could contribute to continuity of care among different care providers, inform patients about their general health status, and aid in policy planning and directing resources.[30,45]

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Appendix 1. Frailty Index deficits

Deficit	Deficit name	Deficit prev.	ICPC[a]	ICPC-Label	Days[b]	Item prev.(%)
1	General complaints	10.6	A01	Pain general/multiple sites	365	2.1
			A04	Weakness/tiredness general	365	4.0
			A05	General deterioration	365	0.4
			A28	Limited function/disability (NOS)	-	0
			B28	Limited function/disability (blood, blood forming)	-	0
			B80	Iron deficiency anaemia	365	1.8
			B81	Anaemia, Vitamin B12/folate def.	365	0.9
			B82	Anaemia other/unspecified	365	0.9
			D28	Limited function/disability (digestive)	-	0.1
			F28	Limited function/disability (eye)	-	0.3
			H28	Limited function/disability (ear)	-	0
			K28	Limited function/disability (circulatory)	-	0
			L28	Limited function/disability (musculoskeletal)	-	0.8
			N28	Limited function/disability (neurological)	-	0
			P28	Limited function/disability (psychological)	-	0
			P78	Neuraesthenia/surmenage	365	0.3
			R28	Limited function/disability (respiratory)	-	0.1
			S28	Limited function/disability (skin)	-	0
			T28	Limited function/disability (metabolic, endocrine, nutrition)	-	0
			U28	Limited function/disability (urinary)	-	0.1
			X28	Limited function/disability (female, genital)	-	0
			Y28	Limited function/disability (male, genital)	-	0
			Z28	Limited function/disability (social)	-	0.1
2	Neoplasm – other	10.9	A79	Malignancy NOS		0
			B72	Hodgkin's disease	-	0.3
			B73	Leukaemia	-	0.3
			B74	Malignant neoplasm blood other	-	0.1
			D74	Malignant neoplasm stomach	-	0.1
			D76	Malignant neoplasm pancreas	-	0.1
			D77	Malig. neoplasm digest other/NOS	-	0.4
			F74	Neoplasm of eye/adnexa	-	0.1
			H75	Neoplasm of ear	-	0
			K72	Neoplasm cardiovascular	-	0

Deficit	Deficit name	Deficit prev.	ICPC[a]	ICPC-Label	Days[b]	Item prev.(%)
			L71	Malignant neoplasm musculoskeletal	-	0.3
			N74	Malignant neoplasm nervous system	-	0
			R84	Malignant neoplasm bronchus/lung	-	0.7
			S77	Malignant neoplasm of skin	-	4.6
			T71	Malignant neoplasm thyroid	-	0.1
			U75	Malignant neoplasm of kidney	-	0.3
			U76	Malignant neoplasm of bladder	-	0.9
			U77	Malignant neoplasm urinary other	-	0.1
			X75	Malignant neoplasm cervix	-	0.2
			X76	Malignant neoplasm breast female	-	2.3
			X77	Malignant neoplasm genital other (f)	-	0.7
			Y78	Malignant neoplasm male genital / mammae	-	0.2
3	Incontinence	11.0	D17	Incontinence of bowel	-	0.9
			U04	Incontinence urine	-	7.3
			X87	Uterovaginal prolapse	-	3.6
4	GI/Liver disease	5.9	D72	Viral hepatitis	-	0.4
			D97	Cirrhosis / liver disease NOS	-	0.9
			D75	Malignant neoplasm colon/rectum	-	1.8
			D85	Duodenal ulcer	365	1.2
			D86	Peptic ulcer other	365	0.9
			D94	Chronic enteritis/ulcerative colitis	-	1.0
5	Oesophagus disease	5.8	D84	Oesophagus disease	365	5.8
6	Visual impairment	9.7	F83	Retinopathy	-	1.6
			F94	Blindness	-	0.4
			F84	Macular degeneration	-	2.6
			F93	Glaucoma	-	5.5
7	Cataract	13.4	F92	Cataract	-	13.4
8	Hearing impairment	8.8	H84	Presbyacusis	-	5.8
			H85	Acoustic trauma	-	0.4
			H86	Deafness	-	2.8
9	Respiratory problems	5.7	K02	Pressure/tightness of heart	365	1.2
			R02	Shortness of breath/dyspnoea w/o K02	365	2.3
			R81	Pneumonia	365	2.4
10	Angina pectoris	11.2	K74	Angina pectoris	365	11.2
11	Myocardial disease	6.3	K75	Acute myocardial infarction	365	5.7
			K76	Other / chronic ischaemic heart disease	-	0.7
12	Heart failure	5.3	K77	Heart failure	-	5.3

Deficit	Deficit name	Deficit prev.	ICPC[a]	ICPC-Label	Days[b]	Item prev.(%)
13	Atrial fibrillation/flutter	8.2	K78	Atrial fibrillation/flutter	365	8.2
14	Hypertension – uncomplicated	35.8	K86	Hypertension uncomplicated	365	35.8
15	Hypertension – complicated	8.8	K87	Hypertension complicated	-	8.8
16	Dizziness	8.1	A06	Fainting/syncope	365	1.6
			H82	Vertiginous syndrome / labyrinthitis	365	4.6
			K88	Postural hypotension	365	0.4
			N17	Vertigo/dizziness	365	1.7
17	TIA / CVA	8.9	K89	Transient cerebral ischaemia	365	3.9
			K90	Stroke/cerebrovascular accident	-	5.2
18	Vascular disease	8.0	K91	Atherosclerosis	-	1.0
			K92	other PVD	-	3.3
			K93	Pulmonary embolism	365	0.7
			K94	Phlebitis/thrombophlebitis	365	1.1
			K99	Cardiovascular disease other	-	2.7
19	Fracture/ Osteoporosis	11.3	A80	Trauma/injury NOS	365	1.1
			L72	Fracture: radius/ulna	365	0.5
			L73	Fracture: tibia/fibula	365	0.5
			L74	Fracture: hand/foot bone	365	0.3
			L75	Fracture: femur	365	0.9
			L76	Fracture: other	365	1.1
			L95	Osteoporosis	-	8.0
20	Arthritis/ Osteoarthrosis	7.7	L88	Rheumatoid arthritis / related condition	-	1.7
			L89	Osteoarthrosis of hip	-	3.6
			L91	Osteoarthrosis other / related condition	-	2.7
21	Osteoarthrosis knee	6.2	L90	Osteoarthrosis of knee	-	6.2
22	Neurologic disease	7.1	N86	Multiple sclerosis	-	0.2
			N99	Neurological disease, other	-	0.7
			N99	Migraine	365	0.9
			N87	Parkinsonism, Parkinson's disease	-	1.3
			N88	Epilepsy	-	1.5
			N94	Peripheral neuritis/neuropathy	-	3.0
23	Depression	8.0	P03	Feeling depressed	365	2.0
			P76	Depressive disorder	365	6.1
24	Sleep disturbance	11.5	P06	Sleep disturbance	365	11.5

Deficit	Deficit name	Deficit prev.	ICPC[a]	ICPC-Label	Days[b]	Item prev.(%)
25	Cognitive impairment	5.6	P20	Memory/concentration/orientation disturbance	365	2.3
			P85	Mental retardation	-	0.1
			P70	Dementia / Alzheimer's disease	-	3.3
26	Psychiatric problems/ Substance abuse	5.1	P71	Organic psychosis other	365	0.5
			P72	Schizophrenia	-	0.1
			P73	Affective psychosis	365	0.4
			P74	Anxiety disorder/anxiety state	365	1.5
			P15	Chronic alcohol abuse	-	1.6
			P16	Acute alcohol abuse	365	0.1
			P17	Tobacco abuse	-	1.1
			P18	Medication abuse	365	0
			P19	Drug abuse	365	0
27	COPD	8.8	R91	Chronic bronchitis / bronchiectasis	-	0.7
			R95	Chronic obstructive pulmonary disease	-	8.1
28	Asthma	5.8	R96	Asthma	-	5.8
29	Skin problems	6.8	S70	Herpes zoster	365	1.5
			S91	Psoriasis	-	1.7
			S97	Chronic ulcer skin	365	3.7
30	Weight problems	4.9	T05	Feeding problem of adult	365	0.1
			T07	Weight gain	365	0.1
			T08	Weight loss	365	1.3
			T83	Overweight	-	0.8
			T82	Obesity	-	2.7
31	Thyroid disorders	6.2	T85	Hyperthyroidism/thyrotoxicosis	365	1.2
			T86	Hypothyroidism/myxoedema	365	5.0
32	Diabetes mellitus	18.8	T90	Diabetes mellitus	-	18.8
33	Urinary disease	7.5	U99	Urinary disease, other	-	7.5
34	Prostate problems	5.4	Y77	Malignant neoplasm prostate	-	2.1
			Y85	Benign prostatic hypertrophy	-	3.3
35	Social problems	5.7	Z01	Poverty/financial problem	365	0.1
			Z03	Housing/neighbourhood problem	365	0.4
			Z04	Social cultural problem	365	0.2
			Z29	Social problem NOS	365	0.4
			Z12	Relationship problem with partner	365	0.5
			Z14	Partner illness problem	365	1.0
			Z15	Loss/death of partner problem	-	3.4
36	Polypharmacy	28.8	-	-	365	28.8

[a] Dutch ICPC-1 version as currently used in general practices. [b] '365 days' indicates that the belonging item is only considered present when registered at least once in the past year. For items without the '365 days' indication, all time presence is considered. prev. = prevalence.

Chapter 4

Assessing frailty in community-dwelling older people: a systematic review of the psychometric properties of the Frailty Index

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In revision

Abstract

Background

To better accommodate for the complex care needs of frail, older people, general practitioners must be capable of easily identifying frailty in daily clinical practice, for example, by using the frailty index (FI). To explore whether the FI is a valid and adequate screening instrument for primary care, we conducted a systematic review of its psychometric properties.

Methods

We searched the Cochrane, PubMed and Embase databases and included original studies focusing on the criterion validity, construct validity and responsiveness of the FI when applied in community-dwelling older people. We evaluated the quality of the studies included using the Quality in Prognosis Studies (QUIPS) tool. This systematic review was conducted based on the PRISMA statement.

Results

Of the twenty studies identified, eighteen reported on FIs derived from research data, one reported upon an FI derived from an administrative database of home-care clients, and one reported upon an FI derived from routine primary care data. In general, the FI showed good criterion and construct validity but lacked studies on responsiveness. When compared with studies that used data gathered for research purposes, the FI score distribution and rate of increase with age were markedly different in the study using routine primary care data.

Conclusions

Our results suggest that the FI is a valid frailty screening instrument. However, further research using routine Electronic Medical Record data is necessary to investigate whether the psychometric properties of the FI are generalizable to a primary care setting and to facilitate its interpretation and implementation in daily clinical practice.

PROSPERO systematic review register number

CRD42013003737

Background

Among other issues, ageing within the population poses a major burden on healthcare due to the increasing prevalence of frailty among older people.[1] Frailty is defined as a state of increased vulnerability due to somatic, environmental or psychosocial factors.[2] To better accommodate for the complex care needs of frail, older people, a transition towards proactive, population-based care is required, which will improve clinical outcomes and cost-effectiveness.[3,4] To facilitate this care transition, general practitioners (GPs) must be capable of identifying frail older patients within their daily clinical practice.

The Frailty Index (FI) is one of the screening tools for frailty.[5] An FI comprises a predefined list of health deficits (e.g. symptoms, signs, impairments, and diseases) that are indicative of frailty. The proportion of deficits present forms the patient's FI score, which can range from zero to one.[6] Different numbers and types of deficits may be used to construct an FI, which enables application in and comparison between different datasets.[7]

There is considerable debate over whether the FI can be used for frailty screening in daily primary care. Some authors have stated that the FI has not been validated in this setting, that the instrument is of limited value due to its perceived complexity, that the FI has only moderate discriminative ability, and that other frailty instruments, such as the Tilburg Frailty Indicator, are more promising.[8-11] Others have argued that the FI is a significant predictor of adverse health outcomes, that it covers all important frailty factors, that it can be easily derived from routine administrative healthcare data, and they have called for further exploration of the FI's merits in primary care.[12-14]

To further assess the potential of the FI as a screening and monitoring instrument for frailty in primary care, knowledge of its characteristics is essential. Therefore, we performed a systematic review of the literature and assessed the psychometric properties of the FI in identifying frailty among community-dwelling older people.

Methods

Search strategy, selection criteria and data extraction

We searched the Cochrane, PubMed, and Embase databases using the terms 'frailty AND (index OR deficit OR deficits OR cumulative OR accumulation)'. We searched for studies published from August 8th, 2001 onwards, which is the publication date of the landmark study presenting the FI concept.[6] The search was limited to studies in English, and databases were searched until October 30th, 2012. The first and third author (ID and GK) screened titles and abstracts independently and selected studies for full-text

assessment. These full-text studies were assessed by the first author for inclusion, and in cases where doubt existed, an independent assessment by the last author (MS) followed. Citations from the included articles were also searched for additional relevant publications by the first author. Eligibility disagreements were resolved by consensus.
Studies were included that met the following criteria: first, the studies focused on an FI. The FI was defined as a list of health deficits for which patients were screened and that provided an FI score that reflected the proportion of deficits present on the predefined list;[6] second, only original research was included that assessed one of the following psychometric properties of the FI: criterion validity, construct validity or responsiveness; third, the studies focused primarily on community-dwelling older people. Studies were excluded when the study population was selected from a nursing home, were hospitalized or were selected because the population had one specific disease in common. Secondary reports of FI datasets that did not report additional psychometric properties were excluded (see appendix 1 for full details of inclusion and exclusion criteria). Based on these predefined criteria, the first author extracted data on general study characteristics, frailty index characteristics and assessed psychometric properties.

Psychometric properties– Definitions

Currently, there is no consensus about a frailty reference standard against which the criterion validity of the FI could be assessed. However, since there is general agreement that the concept of frailty reflects a state of increased vulnerability to adverse health outcomes, criterion validity is defined as the ability of an FI to predict adverse health outcomes.[15] Construct validity refers to the coherence of the FI with other frailty measures or related conditions and constructs, including comorbidity, disability, self-rated health, age, and gender.[15] Responsiveness reflects the ability of the FI to detect clinically important changes over time in the frailty construct (see appendix 1 for a detailed description of the various psychometric properties).[16] In addition, we examined two intrinsic concepts that are not strictly psychometric properties: interpretability, which is defined as the degree to which the FI score can be assigned clinical meaning and utility, which denotes how practical the scale is to use in daily clinical practice.[16,17]

Quality Assessment

Study quality was evaluated using the Quality in Prognosis Studies (QUIPS) tool, which considers six potential domains of bias: inclusion, attrition, prognostic factor measurement, confounders, outcome measurement, and analysis and reporting.[18] Each

domain comprises a number of prompting items, which enable assessment of the domain as having a high, moderate or low risk of bias.

The QUIPS tool was considered the most appropriate quality appraisal tool because, conceptually, the frailty index is a prognostic instrument. We modified three domains of the QUIPS tool. First, in our review, we were interested only in the descriptive, rather than explanatory, relationships of the FI to adverse health outcomes and other measures; thus, we considered the domain 'confounders' irrelevant. Second, the domain 'outcome measurement' only accommodated studies in which the FI correlated with adverse outcomes, i.e., criterion validity studies. We modified this domain such that the QUIPS tool also applied to studies in which the FI was correlated cross-sectionally or longitudinally with other frailty measures or related constructs, i.e., construct validity or responsiveness studies. Third, in the domain 'prognostic factor measurement', we redefined the prompting item 'Valid and Reliable Measurement of Prognostic Factor' as 'Valid and Reliable Construction of Prognostic Factor' because the FI deficit list must be constructed based on specific criteria:[2,19] first, deficits should be acquired and related to health status; thus, 'blue eyes' is not an appropriate deficit whereas 'heart failure' is appropriate; second, deficit prevalence should increase with age; third, deficits should not 'saturate' too early, for example, presbyopia is present in almost all older people, thus, it is not appropriate as a deficit; fourth, the combination of deficits in an FI should cover a range of systems; fifth, the same FI should be used in follow-up measures; and finally, the FI should comprise at least 30 deficits and deficit prevalence should be at least 1%.[2]

Registration

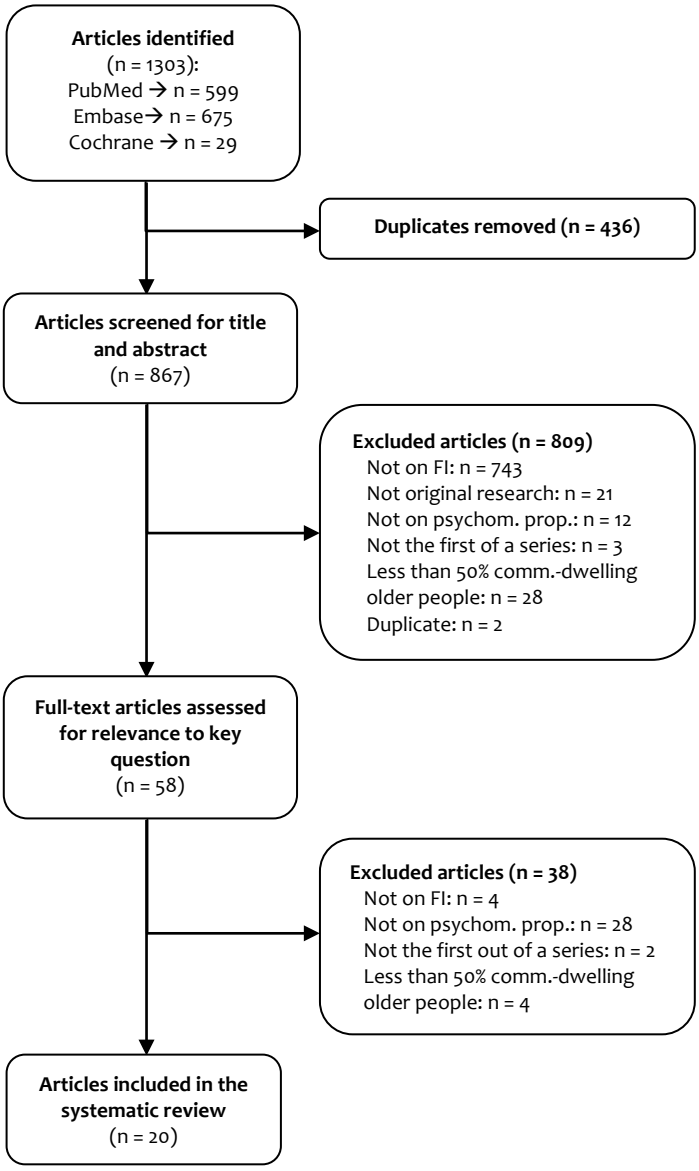
This systematic review was registered prospectively in the PROSPERO international prospective register of systematic reviews (CRD42013003737).

Results

Search Results

After removing duplicates, our search resulted in 867 studies (Figure 1). We excluded 809 studies after screening the titles/abstracts and 38 studies after full-text assessment. We have listed the full bibliographic details and the reason for exclusion of each of these studies (available upon request). No additional studies were found in manual reference searching; thus, we used twenty studies for our final review.

Figure 1. Flowchart of search results



Description of Study Characteristics

One study was a cross-sectional study,[20] and nineteen studies were cohort studies with a follow-up ranging from one to twelve years (Table 1). One study used an administrative dataset of home-care clients,[21] and one study was based on the analysis of routine administrative primary care data.[22] Ten studies were population-based and used a representative sample of independently living or institutionalized older people,[6,23-31] eight studies used community-dwelling samples of only independently living older people,[19,20,22,32-36] and two studies focused specifically on home-care clients or older people in assisted living facilities.[21,37] The number of participants ranged from 754 to 36,424 older people with a mean age varying from 70.1 to 84.9 years, and the percentage of women varied from 50.0 to 76.7%.

The FIs used in the studies were based on 13 to 92 health deficits. Most studies scored deficits dichotomously.[6,21-26,29-31] Eight studies applied multilevel scoring and used,[19,28,32-37] for example, a Likert-scale.[33] Two studies did not report how the deficits were scored.[20,27] Two studies assigned extra weight to predefined deficits,[23,31] for example, to 'polypharmacy'.[31] The mean FI scores varied from 0.13 to 0.26, and except for two studies that reported a lower maximum FI score,[22,31] the maximum reported FI score varied from 0.60 to 0.70.

Table 1. General characteristics of the studies included

Study	Design Data set	Total N (% women) Mean age (yrs ± SD) Setting	Follow-up LTFU	FI deficits			FI scores	
				Deficit number	Deficit scoring	Deficit weighting	Mean / Median (± SD / IQR)	Range
Armstrong et al. (2010)	Retrospective cohort study 8 CCACs	23,952 (69.4%) 81.7 (± 7.4) Home-care clients	1 yr ?	50	B	No	?	?–0.66
Cigolle et al. (2009)	Cross-sectional study HRS	1,657 (55.5%) ? Community-dwelling	N/A	38	?	?	?	?
Drubbel et al. (2012)	Retrospective cohort study GPs EMRs	1,679 (59%) Median 73 (IQR 65-81) Community-dwelling	2 yrs 10.5%	36	B	No	0.08 (0.03-0.14)	0 – 0.42
Fang et al. (2012)	Retrospective cohort study BLSA	3,257 (51.1%) 70.1 (± 9.0) Community-dwelling	8 yrs 13.8%	33	B/M	No	0.13 (± ?)	0 – 0.67
García-González et al. (2009)	Retrospective cohort study MHAS	Total sample: 4,872 Analyzed sample: 4,082 (52.5%) 73 (range 65-105) Community-dwelling	1.95 yrs 13.2%	34	B/M	No	0.16 (± 0.11)	0 – 0.65

Study	Design Data set	Total N (% women) Mean age (yrs ± SD) Setting	Follow-up LTFU	FI deficits			FI scores	
				Deficit number	Deficit scoring	Deficit weighting	Mean / Median (± SD / IQR)	Range
Gu et al. (2009)	Retrospective cohort study CLHLS	13,861 (57.2%) ? (range 65-109) Population-based	3 yrs 12.9%	39	B	Yes	0.26 (± ?)	?
Hogan et al. (2012)	Retrospective cohort study ACCES	1,066 (76.7%) 84.9 (± 7.3) Assisted living residents	1 yr 0%	83[a]	B/M	No	?	?
Kulminski et al. (2008)	Retrospective cohort study CHS	4,721 (? %) ? Population-based	4 yrs 0%	48	B	No	?	0 – 0.70
Kulminski et al. (2007)	Retrospective cohort study NLTCS	24,206 (65.9%) 78.3 (± ?) Population-based	4 yrs ?	32	B	No	0.25 (± ?)	0 – 0.70
Lucicesare et al. (2010a)	Prospective cohort study CSBA	1,016 (55.4%) 74.7 (± 7.1) Population –based	4 yrs 0%	43	B	No	0.14 (± ?)	0 – 0.70
Lucicesare et al. (2010b)	Retrospective cohort study CSHA	1,318 (63.1%) 76.05 (± ?) Population-based	5 yrs	38	?	?	?	0 – 0.59

Study	Design Data set	Total N (% women) Mean age (yrs ± SD) Setting	Follow-up LTFU	FI deficits			FI scores	
				Deficit number	Deficit scoring	Deficit weighting	Mean / Median (± SD / IQR)	Range
Mitnitski et al. (2005)	Retrospective cohort study NPHS, CSHA (3), ALSA, SOPSA, NHANES, H-70, NLTCS-I, ICONS, BCS	36,424 (58.5%) 74 (range: 27 – 105) 7 community-dwelling and 4 clinical / institutional samples	3-12 yrs ?	10 FI's: 38-40 1 FI: 13	B/M	No	?	?
Mitnitski et al. (2001)	Retrospective cohort study CSHA	2,913 (?%) 82 (± 7.4) Population-based	5 yrs ?	92	B	No	?	?
Rockwood et al. (2007b)	Retrospective cohort study CSHA	2,305 (?%) ? Population-based	5 yrs ?	70	B/M	No	?	0 – 0.70
Searle et al. (2008)	Retrospective cohort study YPEP	754 (64.6%) ? Community-dwelling	9 yrs < 10%	40	B/M	No	?	0 – 0.60
Shi et al. (2011)	Retrospective cohort study BLSA	3,257 ((51.1%) 70.1 (± 9.0) Community-dwelling	8 yrs 12.2%	35	B/M	No	?	? – 0.70
Song et al. (2010)	Retrospective cohort study NPHS	2,740 (60.8%) 74 (± 6.6) Population-based	10 yrs 10.1%	36	B	No	0.15 (± ?)	0 – 0.70

Study	Design Data set	Total N (% women) Mean age (yrs ± SD) Setting	Follow-up LTFU	FI deficits			FI scores	
				Deficit number	Deficit scoring	Deficit weighting	Mean / Median (± SD / IQR)	Range
Theou et al. (2012)	Retrospective cohort study CSHA	2,305 (62.1%) 84.6 (± 7.0) Community-dwelling	5 yrs ?	FI 1: 37[b] FI 2: 37[c]	B/M	No	FI 2: 0.24 (± 0.15)	0 – 0.68
Woo et al. (2012)	Prospective cohort study CUHKS	4,000 (50%) ? Community-dwelling	4 yrs 15.9%	47	B	No	?	?
Woo et al. (2006)	Retrospective cohort study HKHS	2,032 (50.8%) ? Population-based	10 yrs 42.4% (3 yrs) 85.3% (10 yrs)	62	B	Yes	0.13 (?-?)	0 – 0.53

? = no information found / unclear; [a] In this study, two FIs were assessed: the Armstrong index and the Full Frailty Index. Only the second FI is reported here (both FIs show similar results); [b] Excluding ADLs / comorbidities, [c] Including ADLs/comorbidities comprising 37 different deficits to FI 1; B = binary scoring; FI = Frailty Index; IQR = Interquartile range; LTFU = Lost to follow-up; M = multilevel scoring; N/A = not applicable; Population-based = representative sample of community-dwelling and institutionalized older people; SD = standard deviation; Data sources: ACCES = Alberta Continuing Care Epidemiological Studies; ALSA = Australian Longitudinal Study of Ageing; BCS = Breast Cancer Survivor Study; BLSA = Beijing Longitudinal Study of Ageing; CCAC = Community Care Access Centre; CHS = Cardiovasculair Health Study; CLHLS = Chinese Longitudinal Healthy Longevity Survey; CSBA = Conselice Study of Brain Ageing; CSHA: Canadian Study of Health and Ageing; CUHKS = Chinese University of Hong Kong Study; GPs EMR = General Practitioners' Electronic Medical Record; H-70 = Gothenburg Study; HKHS = Hong Kong Health Survey; HKSPH = Hong Kong School of Public Health study; HRS = Health and Retirement Survey; ICONS = Improving Cardiovascular Outcomes in Nova Scotia; MHAS = Mexican Health and Aging Study; NHANES = National Health and Nutrition Examination Survey; NLTCS(-i) = National Long Term Care Survey(-institute); NPHS = National Population Health Survey; SOPSA = Sydney Older Persons Studies on Aging; YPEP = Yale Precipitating Events Project.

Quality Assessment

Four studies showed a low risk of bias for each of the five domains considered; fourteen studies showed a moderate-to-high risk of bias in one or two domains; and two studies showed a moderate-to-high risk of bias in three or four domains (Table 2). Risks of bias were highest in the domain of study attrition, which was due to very low response rates or an unclear response rate.[19,25,31,34] In one cohort study, attrition was not assessed because only the cross-sectional study component was considered.[27] For the remaining fourteen cohort studies, losses to follow-up were<16%.

In the domain of prognostic factor measurement, eleven studies were judged as having a moderate risk of bias.[19,20,22,24,27,28,30-32,34,36] Of these eleven studies, four studies did not report their entire FI deficit list,[20,26,27,32] three used data-driven cut-off points for the FI,[24,26,30] and nine did not report the percentage of missing FI data or how missing FI data were managed.[19,20,22,24,30-32,34,36] In the remaining nine studies showing a low risk of bias in the prognostic factor measurement, eight reported a percentage of missing data of <5%,[21,23,25,28,29,33,35,37] and one study did not report the percentage of missing data.[6] Six studies managed missing data by excluding the missing deficits from the denominator when calculating the FI.[6,25,28,32,35,37] Two studies imputed the missing FI data.[23,29] All twenty studies complied with the criteria for adequate FI construction as described in the 'Methods' section.

In total, 98 separate domains were assessed for risk of bias: 5.1% of domains showed high risk, 25.5% of domains showed moderate risk, and 69.4% of domains showed a low risk of bias (full QUIPS appraisal forms for each study are available upon request).

Table 2. Assessment of risk of bias using the 'Quality Assessment in Prognostic Studies' (QUIPS) tool.

Study	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Statistical analysis
Armstrong et al. (2010)	Low	Low	Low	Moderate	Low
Cigolle et al. (2009)	Low	N/A	Moderate	Low	Moderate
Drubbel et al. (2012)	Low	Moderate	Moderate	Low	Low
Fang et al. (2012)	Low	Moderate	Moderate	Low	Low
García-González et al. (2009)	Low	Moderate	Low	Low	Low

Study	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Statistical analysis
Gu et al. (2009)	Low	Low	Low	Low	Low
Hogan et al. (2012)	Low	Low	Low	Low	Low
Kulminski et al. (2008)	Moderate	Low	Moderate	Low	Low
Kulminski et al. (2007)	Low	High	Low	Low	Low
Lucicesare et al. (2010a)	Low	Low	Moderate	Low	Moderate
Lucicesare et al. (2010b)	Low	N/A[a]	Moderate	Low	Low
Mitnitski et al. (2005)	Low	High	Moderate	Low	Low
Mitnitski et al. (2001)	Low	Moderate	Low	Low	Low
Rockwood et al. (2007b)	Moderate	Moderate	Low	Low	Low
Searle et al. (2008)	Low	High	Moderate	Low	Low
Shi et al. (2011)	Low	Low	Low	Low	Low
Song et al. (2010)	Low	Low	Low	Low	Low
Theou et al. (2012)	Low	Moderate	Moderate	Low	Moderate
Woo et al. (2012)	High	Moderate	Moderate	Low	Moderate
Woo et al. (2006)	Low	High	Moderate	Low	Low

Low = low risk of bias; Moderate = moderate risk of bias; High = high risk of bias. [a] Attrition was not assessed because only the cros-sectional component in which construct validity was examined was of interest.

Psychometric properties of the FI

Criterion Validity

Fifteen studies assessed the criterion validity of the FI by evaluating the predictive ability of the FI for mortality, institutionalization, hospitalization, number of days in hospital, morbidity, Emergency Department (ED) visits, out-of-hours GP consultations, falls, fractures, change in ADL score, and change in mental score (Table 3). In each study, the FI was incorporated into a multivariable regression model that was corrected for age, gender and a variety of other co-variables. In each model, the FI was a significant predictor of the assessed outcome.

Twelve studies focused on the prediction of mortality, for which hazard ratios of 1.01(SE ± 0.003; per deficit increase in the frailty index) to 6.45 (95% CI 4.10-10.14, most-frail group (FI score 0.35-0.65) versus the least-frail group (FI score < 0.07) were reported.[33,34] A multivariable model with age, gender, co-morbidity and an FI resulted in an Area Under the Curve (AUC) of 0.691 (95% CI 0.648-0.733) for one-year mortality.[37] Used as a single independent variable, the FI predicted two-year mortality with an AUC of 0.780 (± 0.020 SE) and a ten-year mortality with an AUC of 0.720 (± 0.020 SE).[29]

For other outcome measures, comparable AUCs were as follows: 0.610 (95% CI 0.576-0.644) for one-year hospitalization risk and 0.667 (95% CI 0.625-0.707) for a one-year risk of moving to long-term care.[37] For the prediction of time to the combined outcome of ED/out-of-hours GP surgery visits, nursing home admission and mortality, the c-statistic of the FI used as a single independent variable was 0.686 (95% CI 0.664-0.708). When the FI was combined in a model with age, gender, and consultation gap, the c-statistic improved to 0.702 (95% CI 0.680-0.724).[22]

One study tested the added value of the FI in a multivariable model for predicting adverse health outcomes. For mortality and transition to long-term care, the AUCs of the models including an FI were significantly higher than the AUCs of a model comprising only age, gender and co-morbidity ($p < 0.03$). For hospitalization, the AUC of the full model with age, gender, co-morbidity and an FI was significantly higher than the AUC of a model comprising only age and gender ($p < 0.001$).[37]

Construct validity

Eleven studies evaluated the construct validity of the FI.[6,20,21,24-28,34,36,37] The FI showed a strong positive correlation with the Functional Reach test ($r = 0.73$),[28] Consolice Study of Brain Ageing (CSBA) score ($r = 0.72$),[26] Frailty Phenotype (0.65),[28] and Edmonton Frail Scale (EFS; $r = 0.61$),[21] a strong negative correlation with the Mini Mental State Examination score ($r = -0.58$),[28] and a moderate correlation with the Changes in Health,

End-Stage Disease and Signs and Symptoms (CHESS) Scale (r = 0.35).[21] When the dichotomized FI was compared with the Frailty Phenotype where the latter was used as a reference standard, the FI showed a sensitivity of 45.9 to 60.7% and a specificity of 83.5 to 90.0%.[20,24] When compared with the Functional Domains model, the sensitivity of the FI was 38%, and its specificity was 91.5%.[20] When using a three-level risk categorization, the weighted kappa of the FI compared with the Frailty Phenotype was 0.17 (95% CI 0.13-0.20), and the weighted kappa of the FI compared with the CHESS scale was 0.36 (95% CI 0.31-0.40).

The FI displayed moderate correlation with the concept of self-rated health (r = 0.49), which was expressed as an index of self-rated health deficits.[27] When the crude correlation of the FI was assessed with age, a weak to moderate correlation of 0.193, 0.241 and 0.320, respectively, was reported.[6,25,26] One study compared the age trajectories of the FI score within community-dwelling and institutional/clinical cohorts,[34] with higher levels of comorbidity and disability in the latter. The FI score increased gradually with age in community-dwelling cohorts, whereas the FI score was high at all ages in the institutional/clinical cohorts.

One study examined specifically an FI with only symptoms and signs as deficits and demonstrated that older people with higher FI scores showed more functional impairments in (I)ADL and more co-morbidity than patients with lower FI scores.[36]

Responsiveness, Utility and Interpretability

No studies reported on the responsiveness or the utility of the FI in daily clinical practice. Seven of the studies included reported on the FI score distribution in their entire study sample, and each reported a right-skewed distribution.[6,19,22,23,25,31,33] The FI score distribution shifted towards a normal distribution in populations with higher frailty levels, for example, in older age groups,[23] in a sub-population deceased within one year after a baseline interview,[25] and in a population with Alzheimer's disease.[6]

Without formally assessing correlations within a construct validity context, sixteen studies reported that older people and women show higher FI scores,[6,19,20,22,23,25-37] and only one study reported a lower percentage of women in the most-frail group.[21]

Six studies quantified the increase in FI score with chronological age, of which all reported a similar increase in FI score with age ranging from +0.02 to 0.05/year.[6,19,22,26,34,35]

Table 3. Criterion Validity Results: the Predictive Ability of the Frailty Index for Adverse Health Outcomes.

Study	Outcome variable with events (n)	Model	Factors controlled for in model	Effect measure	95% CI / SE	Interpretation effect measure
Armstrong et al. (2010)	Mortality: 1676 Institutionalization: 4550	Cox proportional hazards regression	Age, gender	FI: HR = 1.93 (EFS: HR = 2.49) (CHESS: HR = 2.32)	1.79-2.08 (2.32-2.68) (2.15-2.51)	Most frail (15%) vs. least frail (60%) group
Drubbel et al. (2012)	Mortality/ED visits/ institutionalization/out-of-hours GP surgery visits: 508	Cox proportional hazards regression	Age, gender, consultation gap	HR = 1.166	1.129-1.210	Per deficit increase in FI
Fang et al. (2012)	Recurrent falls: 109	Logistic regression	Age, gender, education	OR = 1.54	1.34-1.76	Per increment FI
	Recurrent fractures: 174	Logistic regression	Age, gender, education	OR = 1.07	0.94-1.22	Per increment FI
	Mortality: 1101	Cox proportional hazards regression	Age, gender, education, falls, fractures	HR = 1.29	1.25-1.33	Per increment FI
García-González et al. (2009)	Mortality: 279	Cox proportional hazards regression	Age, gender	HR = 6.45	4.10-10.14	Most frail (FI 0.35-0.65) vs. least frail group (0.00-0.07)
Gu et al. (2009)	Mortality: 5,753	Weibull proportional hazards regression	Age, ethnicity, urban-rural residence, SES, family/social connection and support, health practices	Men (65-79): HR = 4.56 Women (65-79): HR = 3.84	0.96 1.01	Most frail vs. least frail quartile

Study	Outcome variable with events (n)	Model	Factors controlled for in model	Effect measure	95% CI / SE	Interpretation effect measure
Hogan et al. (2012)	Mortality: 170	Logistic regression	Age, gender, co-morbidity	RR = 2.35	1.56-3.54	Most frail (FI > 0.30)
	≥ 1 hospitalization: 424	Logistic regression	Age, gender, co-morbidity	RR = 1.28	1.04-1.57	vs. least frail group (FI < 0.20)
	Institutionalization: 204	Logistic regression	Age, gender, co-morbidity	RR = 3.30	2.29-4.76	
Kulminski et al. (2008)	Mortality: 421	Cox proportional hazards regression	Age, gender, FP	FI: RR = 1.035 (FP: RR = 1.014)	1.026-1.045 (1.009-1.019)	Per 1% increment in FI (or FP)
Kulminski et al. (2007)	Mortality: 2146	Cox proportional hazards regression	Age, gender	RR = 1.029	1.001	Per 1% increment in FI
Lucicesare et al. (2010a)	Mortality: 147	Cox proportional hazards regression	Age, gender, CSBA score	FI: HR = 5.26 (CSBA score: HR = 1.52)	1.05-26.42 (1.28-1.81)	?
Mitnitski et al. (2005)	Mortality (% / yr) 3.7-20.6	Cox proportional hazards regression	Age, gender	CSHA-s: HR = 1.031 CSHA-c: HR = 1.054 CSHA-i: HR = 1.046 SOPSA: HR =1.079 NHANES: HR = 1.011	0.003 0.007 0.009 0.022 0.003	Per deficit increase in FI
Searle et al. (2008)	Mortality: ?	Cox proportional hazards regression	Age, gender	HR = 1.03	1.02-1.04	Per 0.01 increase in FI

Study	Outcome variable with events (n)	Model	Factors controlled for in model	Effect measure	95% CI / SE	Interpretation effect measure
Shi et al. (2011)	Mortality: 1,155	Cox proportional hazards regression	Age, gender	HR = 1.13	1.09-1.47	Per deficit increase in FI
Song et al. (2010)	Mortality: 1,208	Cox proportional hazards regression	Age, gender	FI: RR = 1.57	1.41-1.74	Per FI level (FI ≤ 0.08; FI between 0.08-0.25; FI ≥ 0.25).
Theou et al. (2012)	Mortality: 1002	Cox proportional hazards regression	Age, gender, nr. of ADL disabilities, nr. of chronic diseases	FI 1: HR = 1.11	1.06-1.17	Per 0.1 increase in FI
Woo et al. (2006)	Change in ADL score 0-3 yrs[a]	Linear regression	Age, gender, ADL score at baseline	B = -4.99	-7.68 - -2.30	Per 1.0 increase in FI
	Change in mental score 0-3yrs[a]	Linear regression	Age, gender, mental score at baseline	B = -2.23	-4.11 - -0.35	Per 1.0 increase in FI
	Change in hospital days 0-3 yrs[a]	Linear regression	Age, gender, hospital days at baseline	B = 45.74	28.16 – 63.33	Per 1.0 increase in FI
	New diseases at three yrs[a]	Ordinal logistic regression	-	For FI = 0.00, predicted probability ≥ 1 new disease = 17.4% For FI = 0.50, predicted probability ≥ 1 new disease = 52.2%		Predicted probabilities for new diseases at 3 years

[a] Regression models with 3-year outcomes reported due to excess LTFU at 10 years. 95% CI = 95 % Confidence Interval; adm. = admission; ADL = Activities of Daily Living; B = beta; CHESS = Changes in Health, End-Stage Disease and Signs and Symptoms Scale; CSBA = Conselice Study of Brain Ageing; CSHA = Canadian Study of Health and Ageing; DI = Deficit Index (Frailty Index); EFS = Edmonton Frail Scale; FI = Frailty Index; FP = Frailty Phenotype; HR = hazard ratio; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; PBA = Personal Biological Age; RR = relative risk; SE = standard error; SOPSA Sydney Older Persons Studies on Aging.

Discussion

In this systematic review, we demonstrate that the FI adequately predicts a wide range of adverse health outcomes and that its discriminative capability is poor to adequate. The FI correlates strongly with other frailty measures, except for the CHESS scale. However, this scale is not a frailty measure per se but was designed to measure 'health instability' and to specifically predict mortality in institutionalized older people.[38] Typically, the FI shows a right-skewed distribution that shifts towards a normal distribution in frailer groups. The FI score increases steadily with age towards a maximum of 0.60-0.70, indicating that no ceiling effect exists. There is no evidence supporting responsiveness or utility. However, some studies reflected upon the potential utility of the FI and noted two major advantages: first, the FI can be constructed from available data whether from administrative routine primary care data,[22] specific measurements, such as the interRAI-AL instrument,[37] or comprehensive geriatric assessment data.[26,29] Second, the FI score can be calculated using software thereby facilitating its clinical application.[24,37]

Our review has a number of strengths. First, we used a broad, sensitive search strategy with a low risk of missing relevant studies. Thus, we identified a large number of studies with consistent results across a variety of FIs in different populations. Second, we only considered relevant psychometric properties. We omitted reliability because the FI is an automated screening procedure and therefore not susceptible to intra- or interrater variability. Internal consistency was not examined because the FI is a formative model, i.e., the items form the construct together and therefore do not need to be correlated.[39] Third, the definitions used were tailored specifically to those aspects considered essential for frailty measures and based on a standardized taxonomy.[15,16] Fourth, we tailored our detailed inclusion and exclusion criteria to support our aim, which was to select those FI studies relevant for primary care. For example, we excluded studies with an FI based on a comprehensive geriatric assessment because it is not feasible to perform such an assessment for each older patient in primary care. Fifth, we appraised included studies critically using the QUIPS tool, which provided comprehensive quality assessment that demonstrated overall good quality of the methodology used in the included studies. The majority of studies reported sufficient details on their study sample, used appropriate criteria for FI construction, and reported few missing data. Moreover, the reported loss to follow-up was typically well below 20%; thus, biased results were unlikely.[40]

Our review also has several limitations. First, there is a risk of publication bias because studies with negative results are less likely to be published.[41] Because no register exists

for validation studies, publication bias could not be formally assessed. However, the studies included in our review have been performed by various different research groups from all over the world indicating that publication bias is less likely. Second, due to the withdrawal of one of the authors (GK), the first author (ID) performed the full-text assessment and quality appraisal partially alone, which may have caused potential selection bias. However, strict predefined selection and quality appraisal criteria were applied (see additional files 1 and 2), and in cases where doubt existed, full-texts were assessed independently by the last author (MS). Third, most of the included studies on construct validity lacked prespecified hypotheses, which increases the risk of bias because, retrospectively, alternative explanations for low correlations may be sought.[39] Because the majority of correlations were robust, this risk appears limited. Finally, an individual patient data meta-analysis would have been preferable when summarizing research on the criterion validity of the FI. However, because the nature and number of deficits differed between the studies, it was not feasible to merge these data. Moreover, due to study heterogeneity, a meta-analysis on the outcome measures was not possible.[41]

Apart from the FI, another frailty screening instrument that has shown good criterion and construct validity is the Frailty Phenotype.[42] One may question whether this performance-based measure would be preferable to implement in general practice, since it has also good face validity, consisting of five easily interpretable parameters (unintentional weight loss, self-reported exhaustion, weakness, slow walking speed, and low physical activity). However, compared to the FI, the Frailty Phenotype would require extra time and resources to enable execution in daily clinical care, and in direct comparison, the FI has been shown to better predict mortality risk among older people.[24]

Our results are consistent with previous FI reviews that also reported on criterion validity and construct validity of the FI.[7,13,43] Our review updates these findings, and whereas these previous reviews were narrative in nature, our review is the first to systematically review the FI's psychometric properties that are relevant to primary care.

In the majority of the included studies on the FI's criterion validity, its predictive ability for mortality is examined. This does not mean that the FI is meant to be a 'mortality prediction' instrument; rather, by including the FI in a multivariable model including age, the FI score aims to explain the variable vulnerability to adverse health outcomes in people of the same age. This heterogeneity in frailty levels is also reflected by the relatively low correlation coefficients that we found between FI and age; whereas, in general, the correlation coefficient for the mean FI scores versus age was high

(e.g. r = 0.985),[34] the correlation coefficient for the individual FI scores versus age was at maximum 0.320.[26]

To assess the construct validity of the FI, we focused on its correlation with other frailty measures, age, gender, disability, comorbidity, and self-rated health.[15] However, the concordance of the FI with a broad array of other measures has also been investigated, and a high FI score has been demonstrated to correlate with a high and low BMI,[44] smoking,[45,46] impaired psychological well-being,[47] psychiatric illness,[48] impaired mobility,[49] impaired cognition and Alzheimer's disease,[50,51] pain,[52] high levels of gonadotropins,[53] neighborhood deprivation and low individual socio-economic status,[54] rural residence,[55,56] and low education and little social support or participation.[57] The FI may also serve as a basis to calculate 'biological age'. Individuals with an FI score that is relatively high for their age and gender show a biological age that is higher than their chronological age, and this biological age is also a significant predictor of mortality.[58]

In this systematic review we did not find any studies on the FI's responsiveness. One may argue that studies relating FI score change to baseline factors, such as mobility and baseline frailty state, and studies modeling FI score change do describe responsiveness.[49,59] These studies demonstrate that FI score development over time can be adequately described using a time dependent Poisson distribution, and that the probability of improvement, stability and worsening of the FI score is directly related to the baseline number of deficits, age, and mobility status. However, we did not consider these studies as responsiveness studies, since they did not study pre-specified hypotheses regarding the expected correlations between changes in the score on the FI instrument, and changes in other variables, such as scores on other instruments, or demographic or clinical variables.[16] An important finding of our systematic review is that eighteen out of twenty studies explored the FI's psychometric properties in datasets gathered specifically for research purposes. These studies consistently showed a higher maximum FI score compared with the study that investigated the FI using routine primary care data,[22] indicating that the psychometric properties of the FI in data gathered for research purposes cannot be automatically compared with FIs based on routine primary care data. The narrower FI score range in the study using routine primary care data reflects unexpectedly low deficit prevalences, which may be caused by several reasons: first, patients may experience symptoms or problems with which they do not present themselves to the GP; second, there may be suboptimal data registration in the electronic medical record (EMR),[60,61] and third, the FI may need to include more items on level of functioning, mobility or health attitude instead of merely relying on morbidity deficits. Also, except for the polypharmacy deficit, this FI was based

on one single data source out of the EMR, namely symptoms and diagnoses encoded according to the International Classification of Primary Care (ICPC).[62] Care should be taken to construct an FI that captures all information available in the EMR by using, for example, not only ICPC-encoded data but also diagnostic measurement data, such as body mass index or laboratory tests, and elaborate medication data, encoded according to the Anatomic Therapeutic Chemical (ATC).[63]

Conclusions

In this systematic review, the FI demonstrates good criterion and construct validity, but its discriminatory ability is poor to moderate. In general, the FI appears to be an easily interpretable instrument that is practical to manage; however, studies that focus on its responsiveness, interpretability or utility are lacking. These results support the potential of the FI as a screening instrument for frailty in primary care and also demonstrate that further research into its psychometric properties is required. FIs based on research data show different characteristics than those based on routine primary care data. Given its implementation in clinical practice, future validation studies of the FI should focus primarily on its application in routine primary care data.

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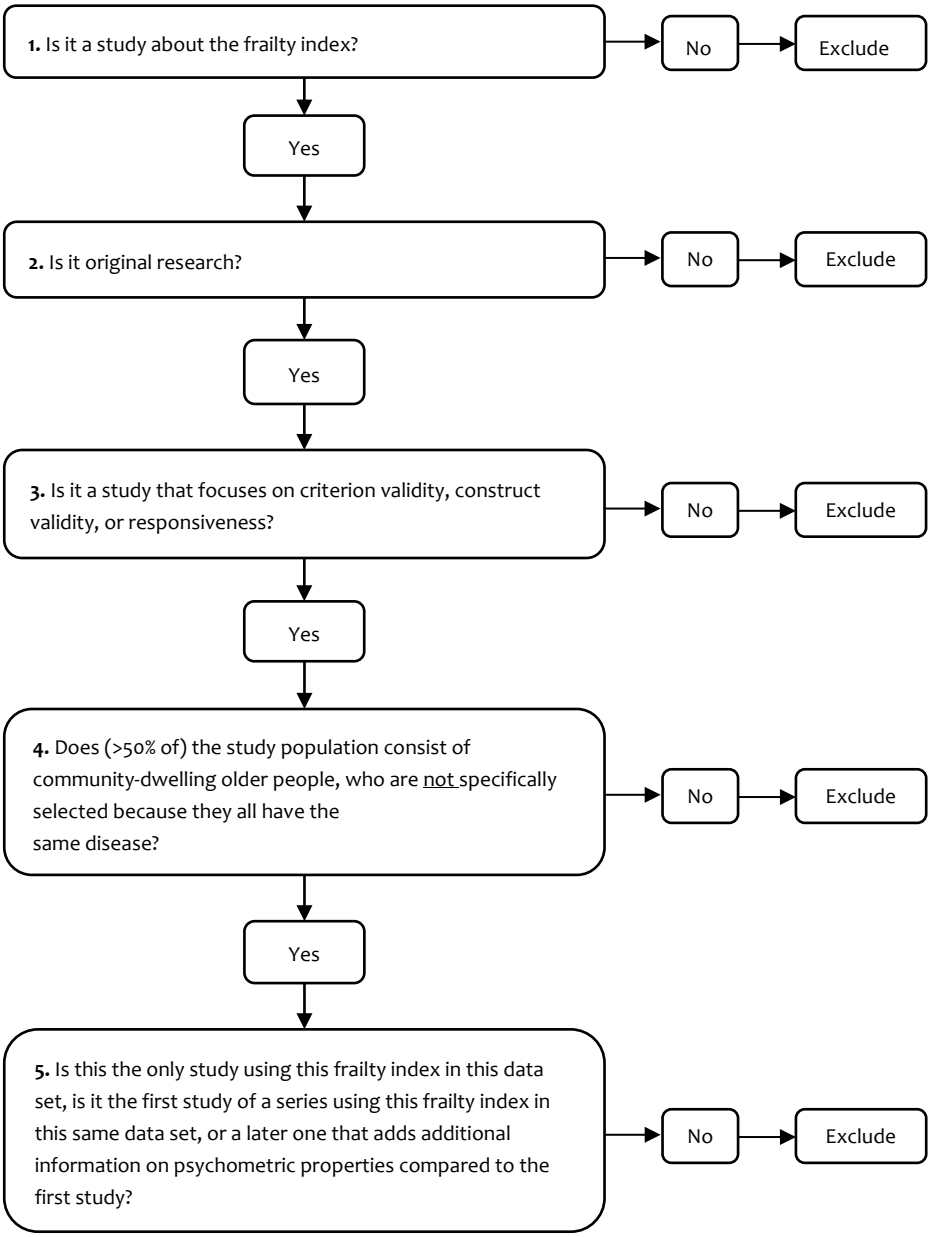
Appendix 1. Eligibility form



Additional information on used eligibility criteria

The frailty index concept as proposed by Mitnitski and Rockwood should be the main focus of the article, or should be one of multiple frailty measures that are compared. In the original concept, the frailty index consists of a list of health deficits. Patients are screened for those deficits, and the resulting frailty index score is the proportion of deficits present out of the predefined list. A frailty index based on a comprehensive geriatric assessment is excluded, because in primary care, performing a CGA for all older patients would not be feasible.

All original research should continue to step 3, irrespective whether it is a cross-sectional, observational, case-control study or trial. Examples of articles not considered as original research are reviews, letters, editorials, and commentaries.

The following definitions of psychometric properties are used:

Criterion validity[1] exists when a new definition or test correctly classifies people according to a referent outcome. The outcome can either be an accepted test of impeccable validity or the prediction of an outcome. No frailty referent standard exists yet, but one means of testing the criterion validity of a definition of frailty would be to assess its ability to predict adverse outcomes. *Example:* predictive ability of the frailty index for death or institutionalization.

Construct validity[1] refers to whether the operational definition coheres with other measures of the phenomenon, related conditions and constructs. Construct validity is typically measured by correlation of the new definition with like measures. We focus on correlation with other frailty measures, disability, co-morbidity, self-rated health, age, and gender. Construct validity studies examining relations of the FI with other measures than the above mentioned should be excluded.

Responsiveness[2] refers to the ability of an instrument to detect clinically important change over time in the construct to be measured. It can be seen as a measure of longitudinal construct validity. Pre-specified hypotheses should have been formulated concerning expected mean differences between changes in groups or expected correlations between changes in the scores on the instrument and changes in other variables, such as scores on other instruments, or demographic or clinical variables. Furthermore, to quantify whether the instrument distinguishes clinically important change from measurement error, the Smallest Detectable Change (SDC) should be related to the Minimal Important Change (MIC). Another adequate measure is the AUC,

which is a measure of the ability to distinguish patients who have and have not changed, according to an external criterion. *Examples:* correlation between change in the frailty index and change in (I)ADL score, difference in change in the frailty index between community-dwelling and institutionalized older people.

Older people are defined as people aged 60 years or older. Community-dwelling is defined as living independently with or without home care, or living in an assisted living facility. Studies in an Emergency Department setting, hospital or nursing home should be excluded, just as studies that specifically focus on a study sample in which older people all have the same disease should be excluded.

If multiple studies use the same frailty index in the same data set, only the first study should be included, unless later studies add information about the psychometric properties of the frailty index.

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Chapter 5

Identifying frailty: do the Frailty Index and Groningen Frailty Indicator cover different clinical perspectives? A cross-sectional study

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Abstract

Background

Early identification of frailty is important for proactive primary care. Currently, however, there is no consensus on which measure to use. Therefore, we examined whether a Frailty Index (FI), based on ICPC-coded primary care data, and the Groningen Frailty Indicator (GFI) questionnaire identify the same older people as frail.

Methods

We conducted a cross-sectional, observational study of 1,580 patients aged ≥ 60 years in a Dutch primary care center. Patients received a GFI questionnaire and were surveyed on their baseline characteristics. Frailty-screening software calculated their FI score. The GFI and FI scores were compared as continuous and dichotomised measures.

Results

FI data were available for 1549 patients (98%). 663 patients (42%) returned their GFI questionnaire. Complete GFI and FI scores were available for 638 patients (40.4%), mean age 73.4 years, 52.8% female. There was a positive correlation between the GFI and the FI (Pearson's correlation coefficient 0.544). Using dichotomised scores, 84.3% of patients with a low FI score also had a low GFI score. In patients with a high FI score, 55.1% also had a high GFI score. A continuous FI score accurately predicted a dichotomised GFI score (AUC 0.78, 95% CI 0.74 to 0.82). Being widowed or divorced was an independent predictor of both a high GFI score in patients with a low FI score, and a high FI score in patients with a low GFI score.

Conclusions

The FI and the GFI moderately overlap in identifying frailty in community-dwelling older patients. To provide optimal proactive primary care, we suggest an initial FI screening in routine healthcare data, followed by a GFI questionnaire for patients with a high FI score or otherwise at high risk as the preferred two-step frailty screening process in primary care.

Background

The frail, older population introduces a heavy burden on primary health care.[1-3] To improve proactive care for this vulnerable group, various frailty measures have been suggested. However, there is a lack of consensus on which measure to use in routine primary care practice.[4-7]

One way of assessing frailty in the primary care setting is with a Frailty Index (FI), which uses readily available data.[8] When interfaced with a patient information database, FI software will automatically screen patients for so-called 'health deficits', including symptoms, diseases, or impairments. The proportion of identified deficits to those in the predefined list is the resulting FI score, a dynamic state variable that adequately reflects the frailty level of an individual.[9,10] Alternatively, another approach to measure frailty in the primary care setting is with a self-assessment questionnaire, such as the 15-item Groningen Frailty Indicator (GFI). The GFI questionnaire screens for self-reported limitations and is widely used in The Netherlands.[11] Higher scores indicate higher frailty levels and an increased need for integrated care.[12]

Both the FI and the GFI are feasible for use in primary care. To compute an FI score, center-specific software is needed, which requires financial investment for development and training. Thereafter, limited time is necessary for the generation of frailty reports from the Electronic Medical Records (EMR) data. Conversely, implementation of the GFI questionnaire requires less start-up expenses, but the post-screening process is more time demanding. Apart from logistical differences, also the clinical perspective of these two measures may be different. Whereas the FI score predicts patients' risk of adverse health outcomes, the GFI score reflects current problems in patients' daily lives. To our knowledge, no previous study has examined whether these frailty measures, regardless of individual focus, will identify the same population as frail.[13] Therefore, the aim of this study is to assess if, in community-dwelling older adults, an FI based on ICPC- and ATC-coded routine primary care data and the GFI will identify the same older patients as frail.[14,15]

Methods

Ethical Approval

This study was approved by the Institutional Review Board of the University Medical Center Utrecht, The Netherlands (reference number 10-149/O). Written informed consent was obtained from all patients.

Design

Cross-sectional, observational study conducted in a primary care setting.

Setting

Patients were enrolled from an urban primary care center with seven general practitioners (GPs) managing 10,500 patients in Utrecht, The Netherlands.

Participants

Participants were selected from the center's electronic medical record (EMR) data file. The EMR contained patient information dated through 20 May 2011. All patients 60 years of age and older were eligible for inclusion in the study.

Procedures

On 9 May 2011, the GPs sent all eligible patients a patient information letter, an informed consent form, and a questionnaire. This questionnaire consisted of the Groningen Frailty Indicator (see appendix 1: Groningen Frailty Indicator) as well as questions regarding age, sex, ethnicity, education, and marital status. Patients were included if they returned the informed consent form and questionnaire within three weeks. No reminders were sent.

Concurrent to the mailing of questionnaires, frailty-screening software was interfaced with an anonymous EMR data file to calculate the FI score for each patient. Additionally, this software systematically extracted data on age, gender, and consultation gap, defined as the total number of days from a patient's last contact with the GP until the EMR snapshot date. This timeframe was determined by searching for the most recently registered ICPC code, with the exception of influenza vaccination. We only considered the gap till the last consultation, and did include earlier consultation patterns. In general, age, gender, and care avoidance are related to frailty and a greater risk of adverse health outcomes.[16, 17] Therefore, in addition to the aforementioned questions, these parameters were included as baseline characteristics for our population.

The frailty-screening software uploaded the EMR data to a highly protected server where frailty reports were created prior to being routed to the primary care center. During this process, an external 'trusted third party' routing created pseudonyms to encode personal data so that data processing was completely anonymous outside the primary care center. Included patients consented to the procedure that the researchers would ask the primary care center for all variables that the frailty-screening software

calculated. Frailty report data for the remaining patients of the primary care center were anonymously released into a non-responder data file.

Measurements

GFI

The GFI is a validated, 15-item questionnaire with a score range from zero to fifteen that assesses the physical, cognitive, social, and psychological domains. A GFI score of four or greater is considered the cut-off point for frailty.[11] The GFI has demonstrated high internal consistency and construct validity when compared to the Tilburg Frailty Indicator and the Sherbrook Postal Questionnaire.[13]

Frailty Index

We used a frailty index that we developed in a previous frailty index validation study in the same primary care center.[18] In short, we first selected 140 relevant ICPC-coded items and an ATC-coded polypharmacy item. This selection was based on the literature on FI construction, data on age-related deficit prevalence and health burdens, and a consensus meeting with a local expert group of GPs.[19-22] The ICPC-coded items reflect a range of symptoms, diseases, functional impairments and social problems. Second, to reach a deficit prevalence of at least 5%, we arranged these items into single- and multi-item deficits. Being aware of the commonly employed lower limit for deficit prevalences of 1%, we opted for 5% because of the relatively low prevalence of our separate ICPC-coded items. Furthermore, multi-item deficits needed to reflect a clinically relevant combination of ICPC-coded items. The total selection and arrangement procedure resulted in an FI with 36 deficits (see appendix 2). In the baseline EMR data, the frailty software screened all patients for deficits. For some deficits, e.g., stroke, all available data for each patient were screened. For others, e.g., pneumonia, only data from the past year were considered. This strategy enables deficits to transition from 'present' to 'absent' in follow-up FI assessments, so that improvement of the FI score becomes possible over time. An ICPC-encoded deficit was present when at least one related ICPC code was registered. For single-item deficits such as 'Heart failure', this implied a positive ICPC-encoded item 'K77 – Heart failure'. For multi-item deficits such as 'Hearing impairment', one or more of the three related ICPC-encoded items ('H84 – Presbyacusis', 'H85 – Acoustic trauma', or 'H86 – Deafness') were required to be positive. To calculate the polypharmacy deficit, defined as at least five different medications in chronic use, the frailty software screened for ATC codes. Three prescriptions in the past year with at least one prescription in the last six months was considered as medication in chronic

use. The FI score was defined as the proportion of deficits present. For example, 12 deficits out of 36 provided a FI score of 0.33. Based on the results of the previous validation study in this primary care center, patients with an FI score of 0.08 or higher were considered as frail in the current study. In that validation study, ROC analysis demonstrated a sensitivity of 77.6 percent and a specificity of 53.5 percent for predicting adverse health outcomes (Emergency Room visits, out-of-hours GP consults, nursing home admission, and mortality) at the cut-off value of 0.08, which was considered optimal.[18]

Statistical methods

First, we calculated the descriptive statistics for baseline characteristics for the total population, for the patients grouped according to a high (≥ 4) and low (< 4) GFI score, and for the patients grouped according to a high (≥ 0.08) and low (< 0.08) FI score. Next, we constructed histograms of the distributions of the GFI and FI scores. The strength of the correlation between the FI and the GFI was calculated with Pearson's correlation coefficient, and shared variance was calculated with R^2. Patients were then categorised in a contingency table according to their dichotomised FI and GFI scores. Key baseline characteristics were determined for these four groups, and differences were examined between the two discrepant groups (high GFI score and low FI score; low GFI score and high FI score). Additionally, multivariate logistic regression analyses were performed to determine which baseline characteristics independently predicted this incongruence. Receiver Operator Curve (ROC) analyses were completed with the FI score as a continuous measure and the GFI score as a dichotomised variable. Finally, the mean scores for each of the four GFI sub-domains were compared between high and low FI score groups. Where appropriate, differences between groups were tested with the Pearson Chi-Square test or the Independent Samples t-test, with a p-value of < 0.05 considered significant. Analyses were performed with SPSS version 18 (SPSS, Chicago, IL).

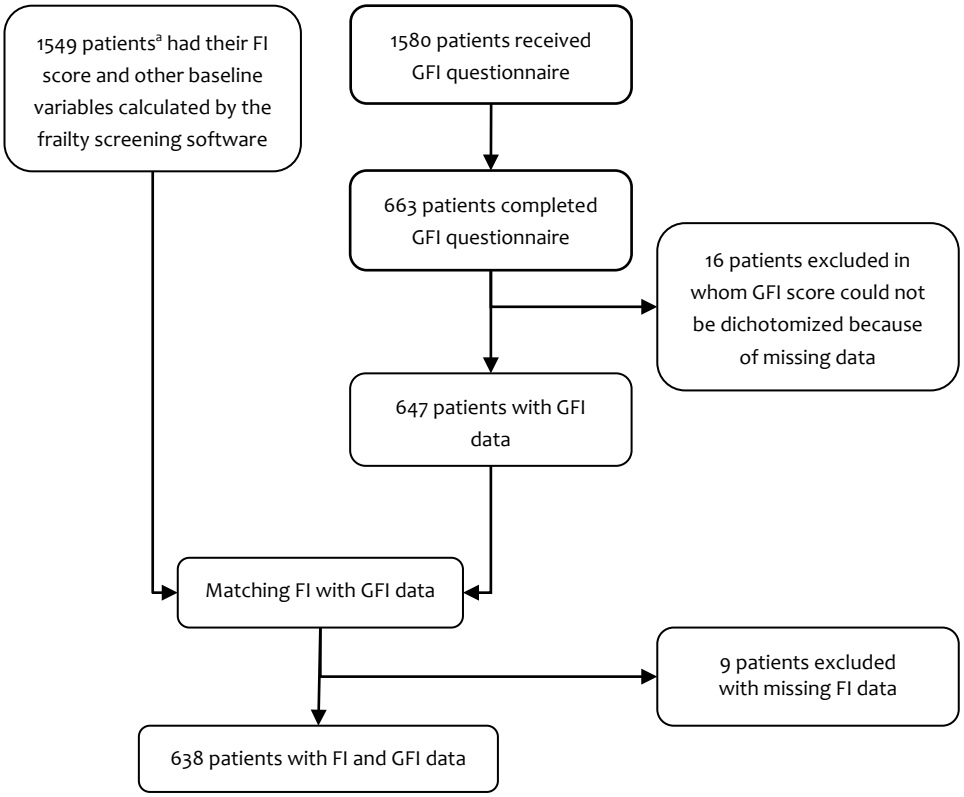
Results

Out of 1580 eligible patients, we were able to calculate an FI score for 1549 patients (98%), and 663 patients (42%) returned the GFI questionnaire. Thus, we had 638 patients (40.4%) with complete GFI and FI data (Figure 1). Non-responders and excluded patients (N=911) were younger than the included population (mean age non-responders and excluded patients: 71.4 years ± 9.4 SD, mean age included patients: 73.4 years ± 9.2 SD, p-value < 0.001), but they did not differ in gender, FI score, or consultation gap.

When grouped by GFI score, patients with GFI scores of four or greater were older, had higher FI scores, and shorter consultation gaps than patients with a GFI score below four (Table 1). Furthermore, patients with high GFI scores more often lived alone as a widow or following divorce, and they were less often highly educated. These trends were similar in patients grouped by FI score.

Both the FI and GFI scores showed a left-skewed distribution in the study sample (Figure 2). The GFI and FI scores showed a moderate positive, linear correlation (Pearson's correlation coefficient = 0.544, p-value < 0.001). In patients aged 60-70 years old, Pearson's correlation coefficient was 0.522 ($p < 0.001$), and in patients aged 80 years and older, Pearson's correlation coefficient was 0.431 ($p = 0.001$). Next, we constructed a contingency table using a cut-off value for frailty of 0.08 for the FI, and four for the GFI. With these dichotomised scores, 84.7% of patients with a low FI score also had a low GFI score. In patients with a high FI score, 55.1% also had a high GFI score (Table 2a). When key baseline characteristics were compared between the two discrepant groups in the contingency table, patients in the group with a low FI score and a high GFI score were more often female, and were more often living alone as a widower or after a divorce than patients with a high FI score and a low GFI index score (Table 2b). Using multivariate logistic regression, we found that in patients with a low FI score, living alone as a widower or after a divorce increased the risk of having a high GFI score. In patients with a low GFI score, older age and living alone as a widower or after a divorce increased the risk of having a high FI score (Table 3). Patients with high FI scores had higher mean scores on the physical, cognitive, social, and psychological domains of the GFI than patients with low FI scores (Table 4). The ROC analysis demonstrated that we could adequately predict that a randomly selected patient from the high-GFI-score group would also have a high FI score (AUC 0.78, 95% CI 0.74 to 0.82).

Figure 1. Flowchart of patient recruitment



[a] Of 31 patients who were born between 1 January 1951 and 30 June 1951, EMR data could not be screened by the frailty-screening software. For the pseudonymisation of personal data, birth dates were set to 1 July of the patients' birth year. Consequently, these 31 patients were not considered as ≥ 60 years of age.

Table 1. Baseline characteristics for the total study population, and for high and low GFI and FI groups

	Total (n = 638)	GFI < 4 (n = 388)	GFI ≥ 4 (n = 250)	p-value	FI < 0.08 (n = 255)	FI ≥ 0.08 (n = 383)	p-value
Age, mean (SD)	73.4 (9.2)	70.9 (8.2)	77.3 (9.4)	< 0.001[b]	68.7 (7.6)	76.6 (8.9)	< 0.001[b]
Females, n (%)	337 (52.8)	195 (50.3)	142 (56.8)	0.11[c]	138 (54.1)	199 (52)	0.59[c]
Frailty index score, mean (SD)	0.11 (0.08)	0.08 (0.06)	0.15 (0.08)	< 0.001[b]	0.03 (0.02)	0.15 (0.07)	< 0.001[b]
Consultation gap in days, mean (SD)	114 (347)	152 (436)	55 (81)	0.001[b]	203 (531)	55 (67.0)	< 0.001[b]
Dutch nationality, n (%)	604 (94.7)	370 (95.4)	234 (93.6)	0.33[c]	244 (95.7)	360 (94.0)	0.35[c]
Social situation							
Living alone, n (%)	56 (8.8)	28 (7.2)	28 (11.2)	0.083[c]	23 (9.0)	33 (8.6)	0.86[c]
Living with a partner, n (%)	370 (58.0)	270 (69.6)	100 (40.0)	< 0.001[c]	176 (69.0)	194 (50.7)	< 0.001[c]
Widowed or divorced, n (%)	207 (32.4)	89 (22.9)	118 (47.2)	< 0.001[c]	54 (21.2)	153 (39.9)	< 0.001[c]
Missing, n (%)	5 (0.8)	1 (0.3)	4 (1.6)	0.061[c]	2 (0.8)	3 (0.8)	1.0[c]
Education (highest finished education)							
None or primary school, n (%)	103 (16.1)	48 (12.4)	55 (22.0)	0.001[c]	32 (12.5)	71 (18.5)	0.044[c]
Secondary school, n (%)	348 (54.5)	208 (53.6)	140 (56.0)	0.55[c]	128 (50.2)	220 (57.4)	0.072[c]
Higher education, n (%)	181 (28.4)	129 (33.2)	52 (20.8)	0.001[c]	92 (36.1)	89 (23.2)	< 0.001[c]
Missing, n (%)	5 (0.8)	3 (0.8)	3 (1.2)	0.97[c]	3 (1.2)	3 (0.8)	0.36[c]
GFI score, mean (SD)[a]	3.2 (2.8)	1.4 (1.1)	6.2 (2.0)	< 0.001[b]	1.8 (1.9)	4.2 (2.8)	< 0.001[b]
GFI score ≥ 4, n (%)	250 (39.2%)	-	-	-	39 (15.3)	211 (55.1)	< 0.001[c]

[a] n total population = 623 for calculation of median GFI score because of patients in whom it could be determined with certainty whether they had a GFI score ≥ 4, 15 had missing values for some GFI questions. [b] Differences were evaluated with the Independent Samples t-test. [c] Differences were evaluated with the Pearson Chi-Square test. FI = frailty index.

Figure 2. FI and GFI frequency distributions

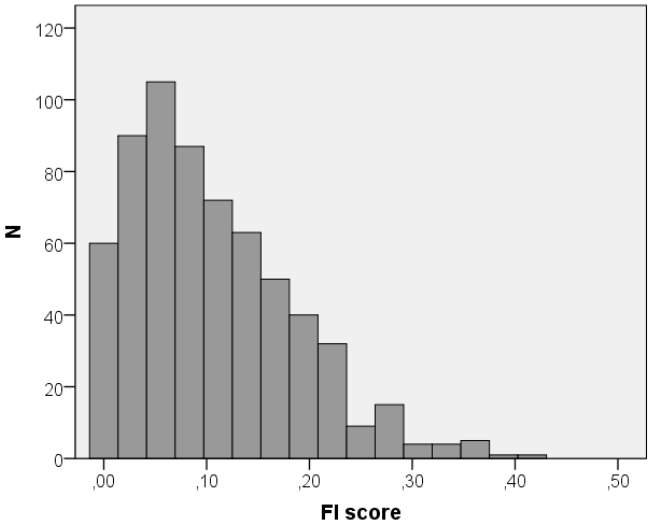


Figure 2A. FI frequency distribution

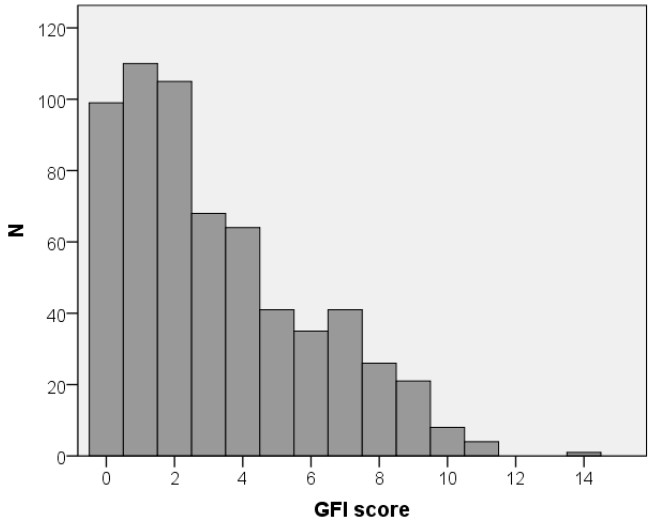


Figure 2B. GFI frequency distribution

Table 2a. Two by two contingency table of FI versus GFI

	GFI ≥ 4	GFI <4	Total
Frailty index ≥ 0.08	211 (55.1%)	172 (44.9%)	383 (100%)
Frailty index < 0.08	39 (15.3%)	216 (84.7%)	255 (100%)
Total	250	388	638

Table 2b. Key characteristics based on FI-GFI group

	Group 1: FI < 0.08 & GFI < 4	Group 2: FI ≥ 0.08 & GFI ≥ 4	Group 3: FI ≥ 0.08 & GFI < 4	Group 4: FI < 0.08 & GFI ≥ 4	Comparison of groups 3 and 4: p-value
N (%)	216 (33.9)	211 (33.1)	172 (27.0)	39 (6.1)	-
Age, mean (SD)	68.0 (7.2)	78.2 (9.3)	74.6 (8.0)	72.4 (8.6)	0.12[a]
Females, n (%)	117 (52.2)	111 (53.6)	80 (48.8)	29 (67.4)	0.011[b]
Consultation gap in days, mean (SD)	222 (571)	47 (54)	65 (78)	96 (160)	0.075[a]
Living alone as a widower or after divorce, n (%)	35 (16.2)	99 (46.9)	54 (31.4)	19 (48.7)	0.040[b]
Primary education or less, n (%)	25 (11.6)	48 (22.7)	23 (13.4)	7 (17.9)	0.46[b]

[a] Differences were evaluated with the Independent Samples t-test. [b] Differences were evaluated with the Pearson Chi-Square test.

Table 3. Independent predictive capacity of baseline characteristics for a high GFI or FI score

Multivariate analysis I (prediction of high GFI score in patients with a low FI score)			
	Odds Ratio	**95% CI**	**p-value**
Age	1.042	0.996– 1.090	0.072
Sex	1.847	0.831 – 4.105	0.13
Consultation gap in months	0.958	0.889 – 1.033	0.27
Living alone as a widower or after divorce	3.797	1.760 – 8.194	0.001
Primary education or less	1.010	0.363 – 2.809	0.99
Multivariate analysis II (prediction of high FI score in patients with a low GFI score)			
	Odds Ratio	**95% CI**	**p-value**
Age	1.059	1.023 – 1.097	0.001
Sex	0.998	0.576 – 1.729	0.99
Consultation gap in months	0.923	0.848 – 1.004	0.062
Living alone as a widower or after divorce	2.149	1.122 – 4.114	0.021
Primary education or less	0.689	0.315 – 1.509	0.35

Effects are depicted per year increase in age and per month increase in consultation gap. Male sex, not living alone as a widower or after divorce, and having other education above primary education were taken as the reference values. CI = confidence interval

Table 4. Mean GFI domain scores per FI group

	FI < 0.08 n = 255	FI ≥ 0.08 n = 383	Significance p-value
Physical GFI domain			
n	250	378	
mean (SD)	0.60 (0.95)	1.90 (1.55)	< 0.001[a]
Cognitive GFI domain			
n	254	380	
mean (SD)	0.26 (0.44)	0.47 (0.50)	< 0.001[a]
Social GFI domain			
n	254	378	
mean (SD)	0.47 (0.87)	1.10 (1.18)	< 0.001[a]
Psychological GFI domain			
n	255	381	
mean (SD)	0.42 (0.72)	0.79 (0.86)	< 0.001[a]

[a] Differences were evaluated with the Independent Samples t-test. Numbers per group differ because 15 patients have incomplete data on one or more GFI domains. Number of questions and score range Per domain: Physical domain: 9 questions, score range 0-9; Cognitive domain: 1 question, score range 0-1; Social domain: 3 questions, score range 0-3, Psychological domain: 2 questions, score range 0-2.

Discussion

Summary

In this study, we demonstrated that, whereas both measures are extensively validated with regard to their measurement of the frailty concept, the FI based upon routine primary care data and the GFI only moderately overlap in the identification of frailty in older patients in the primary care setting.[9, 23, 24] Whereas most patients with few health deficits also report few problems in their daily lives, just over half of patients with multiple health deficits also report having multiple problems in their daily lives. This result illustrates that the FI and GFI cover different aspects or stages of frailty. This is supported by the results of a recent study demonstrating that ADL impairment in bathing, cooking and managing medication occurred only in about 25% of participants with a high FI score.[25] However, there may also be confounding factors that influence the correlation between the FI and the GFI, for example, the variation in self-management abilities between patients.[26] Furthermore, the GFI is a self-report instrument. Certain coping strategies or cognitive impairments might prompt the patient to report fewer problems than might actually exist, distorting the relationship

between the GFI and FI. Finally, social vulnerability may influence the observed correlation between the FI and GFI, as a recent study demonstrated an increased absolute mortality risk in fit people with increased social vulnerability.[27] This is in line with the observation in our study that living alone as a widower or after a divorce is associated with high FI and GFI scores.

Strengths and limitations

Our study has several strengths. First, we investigated two multifactorial frailty measures that are easy to implement in daily practice, both which could serve as an initial screening tool before a comprehensive geriatric assessment.[2] Thus, our study, which was conducted with a representative sample of community-dwelling older patients, has relevant and generalisable results.[28] Second, we demonstrated that the FI and GFI are related to several baseline factors that themselves are linked to frailty, supporting the validity of both measures.[5] Third, we demonstrated that patients with high FI scores have higher mean scores on all GFI domains, not only on the physical GFI domain. Finally, 39% of our patients had a GFI score of four or higher, which is comparable to the 39-46% found in previous studies.13,26

Our study also has some limitations. First, some selective response may have occurred among first generation immigrants due to illiteracy or a language barrier. Since these patients report more chronic conditions and a poorer self-rated health, the correlation between the FI and GFI may have been stronger in this subgroup.29 Second, the 'oldest old' may experience a greater decrease in daily functioning with fewer deficits than the 'youngest old', resulting in a weaker correlation between the GFI and FI. This was confirmed by a lower Pearson's correlation coefficient in patients of 80 years and older, compared to patients aged 60-70 years old. Third, our response rate was 42%. This was lower than the 77% response rate in a comparable population after one reminder13, but comparable to the response rate of 45% in a third study that did not send reminders.26 The low response rate illustrates the practical limitations of the use of the GFI as a first step in frailty screening, but with the use of reminders, the GFI appears feasible in daily practice. Fourth, to define frailty we used a cut-off score of four for the GFI.12, 26 However, this cut-off score may also include 'pre-frail' patients and may be a reason to raise the minimum score for frailty.30 Furthermore, our FI score cut-off value of 0.08 was based on a previous study in the same primary care center, in which we were the first to develop the FI measure from routine primary care data.18 The use of routine primary care data resulted in a narrower FI score range compared to that in other studies.9 Both an unexpectedly low prevalence of deficits identified in routine

healthcare data and the fact that this study's FI consists almost exclusively of comorbidities may have contributed to this narrow score range, and the FI and its cut off values may need to be adjusted accordingly. Finally, cognitive loss is not always identified as a deficit as a result of the corresponding ICPC codes not being registered properly. Because cognitive problems are strongly related to frailty, encoding in routine practice requires careful attention.31, 32

Comparison with existing literature

Depending on the definition, the prevalence of frailty varies widely from 5% to 58%.[33] Some recent studies have demonstrated the continued lack of consensus in defining frailty and the limited value of currently available frailty measures for screening and diagnosis in daily practice.[34, 35] However, others have concluded that the FI seems best suited for clinical use, and that an FI based on ICPC coded primary care data is associated with the risk of adverse health outcomes.[18, 36] Screening and early, proactive care is essential, and with currently available frailty measures, identification of frailty does enable targeted interventions in primary care.[37, 38, 39] By exploring, for the first time, the relationship between the GFI and an FI score derived from routine healthcare data, our results contribute to the development of a frailty-screening strategy that meets the needs of primary care providers.

Implications for research and practice

Taking the different focus of the FI and the GFI into account, we hypothesize that a two-step frailty-screening strategy could be useful to provide optimal proactive primary care for older patients. For several reasons, the FI would be the preferred first step; it uses administrative data readily available for all patients, it can be implemented as an easy-to-use software application in daily clinical practice, and it adequately predicts adverse health outcomes.[9, 18] As a second step, the GFI could identify patients who also experience multiple problems in daily life besides having a high FI score. The response rate of 42% in our study is suboptimal for implementing the GFI as a frailty screening measure, and needs to be improved. However, a previous study using one reminder demonstrated a response rate of 77%. In addition, the GFI could be filled in by patients while visiting the GP, which will increase response rate as well. In patients with a high FI score and low GFI score, evaluation by the GP, reviewing medication and consultation pattern, will be sufficient. Patients with high scores on both measures might benefit from a comprehensive geriatric assessment and tailored, proactive care by a geriatric nurse. Some may question the complexity of this approach, as GFI questionnaire data

may also be incorporated as deficits in the FI score. However, we think the sequential two step screening approach is the most efficient approach to personalised elderly care. Implementing GFI screening only for patients with a high FI score would result in a considerably lower work load of posting questionnaires, sending reminders, or filling in questionnaires together with patients in the primary care center, while our results show that this approach would still identify the majority of patients with a high GFI score. Second, a two-step screening process would enable the primary care practices to carefully allocate geriatric nursing care resources to those patients in highest need, as reflected by a high GFI score.

The only restriction of this approach is that patients that do not return the GFI questionnaire must be followed up because they might be care avoiders. In the U-PROFIT trial, we are currently examining the effect of this two-step screening strategy on the quality of life and daily functioning of frail older people.[40]

Conclusions

The FI and the GFI moderately overlap in identifying frailty in community-dwelling older patients. To provide optimal proactive primary care, we suggest an initial FI screening in routine healthcare data, followed by a GFI questionnaire for patients with a high FI score or otherwise at high risk as the preferred two-step frailty screening process in primary care.

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Appendix 1. Groningen Frailty Indicator questionnaire

1. Are you able to carry out these tasks single-handedly and without any help? (The use of help resources such as a walking stick, walking frame or wheelchair is considered to be independent.)

Shopping

☐ yes
☐ no

Walking around outside (around the house or to the neighbours)

☐ yes
☐ no

Dressing and undressing

☐ yes
☐ no

Going to the toilet

☐ yes
☐ no

2. What mark do you give yourself for physical fitness? (Scale 0 to 10)
Circle the number:

0 1 2 3 4 5 6 7 8 9 10

3. Do you experience problems in daily life due to poor vision?

☐ yes, a lot of problems
☐ yes, some problems
☐ no, no problems

4. Do you experience problems in daily life due to being hard of hearing?

☐ yes, a lot of problems
☐ yes, some problems
☐ no, no problems

5. During the last 6 months have you lost a lot of weight unwillingly?
(3 kg in 1 month or 6 kg in 2 months)

☐ yes
☐ no

6. Do you take 4 or more different types of medicine?

☐ yes
☐ no

7. Do you have any complaints about your memory?

☐ yes
☐ sometimes
☐ no

8. Do you sometimes experience emptiness around yourself?

☐ yes
☐ sometimes
☐ no

9. Do you sometimes miss people around yourself?

☐ yes
☐ sometimes
☐ no

10. Do you sometimes feel abandoned?

☐ yes
☐ sometimes
☐ no

11. Have you recently felt downhearted or sad?

☐ yes
☐ sometimes
☐ no

12. Have you recently felt nervous or anxious?

☐ yes
☐ sometimes
☐ no

Scoring:
Questions 1: Yes = 0; No = 1
Question 2: 0-6 = 1; 7-10 = 0
Questions 3-6: No = 0; Yes = 1
Question 7: No = 0; Sometimes = 0; Yes = 1
Questions 8-12: No = 0; Sometimes = 1; Yes = 1

Appendix 2. Frailty Index deficits

Deficit	Deficit name	Deficit prev.(%)	ICPC[a]	ICPC-Label	Days[b]	Item prev.(%)
1	General complaints	10.6	A01	Pain general/multiple sites	365	2.1
			A04	Weakness/tiredness general	365	4.0
			A05	General deterioration	365	0.4
			A28	Limited function/disability (NOS)	-	0
			B28	Limited function/disability (blood, blood forming)	-	0
			B80	Iron deficiency anaemia	365	1.8
			B81	Anaemia, Vitamin B12/folate def.	365	0.9
			B82	Anaemia other/unspecified	365	0.9
			D28	Limited function/disability (digestive)	-	0.1
			F28	Limited function/disability (eye)	-	0.3
			H28	Limited function/disability (ear)	-	0
			K28	Limited function/disability (circulatory)	-	0
			L28	Limited function/disability (musculoskeletal)	-	0.8
			N28	Limited function/disability (neurological)	-	0
			P28	Limited function/disability (psychological)	-	0
			P78	Neuraesthenia/surmenage	365	0.3
			R28	Limited function/disability (respiratory)	-	0.1
			S28	Limited function/disability (skin)	-	0
			T28	Limited function/disability (metabolic, endocrine, nutrition)	-	0
			U28	Limited function/disability (urinary)	-	0.1
			X28	Limited function/disability (female, genital)	-	0
			Y28	Limited function/disability (male, genital)	-	0
			Z28	Limited function/disability (social)	-	0.1
2	Neoplasm – other	10.9	A79	Malignancy NOS		0
			B72	Hodgkin's disease	-	0.3
			B73	Leukaemia	-	0.3
			B74	Malignant neoplasm blood other	-	0.1
			D74	Malignant neoplasm stomach	-	0.1
			D76	Malignant neoplasm pancreas	-	0.1
			D77	Malig. neoplasm digest other/NOS	-	0.4
			F74	Neoplasm of eye/adnexa	-	0.1
			H75	Neoplasm of ear	-	0
			K72	Neoplasm cardiovascular	-	0

Deficit	Deficit name	Deficit prev.(%)	ICPC[a]	ICPC-Label	Days[b]	Item prev.(%)
			L71	Malignant neoplasm musculoskeletal	-	0.3
			N74	Malignant neoplasm nervous system	-	0
			R84	Malignant neoplasm bronchus/lung	-	0.7
			S77	Malignant neoplasm of skin	-	4.6
			T71	Malignant neoplasm thyroid	-	0.1
			U75	Malignant neoplasm of kidney	-	0.3
			U76	Malignant neoplasm of bladder	-	0.9
			U77	Malignant neoplasm urinary other	-	0.1
			X75	Malignant neoplasm cervix	-	0.2
			X76	Malignant neoplasm breast female	-	2.3
			X77	Malignant neoplasm genital other (f)	-	0.7
			Y78	Malignant neoplasm male genital / mammae	-	0.2
3	Incontinence	11.0	D17	Incontinence of bowel	-	0.9
			U04	Incontinence urine	-	7.3
			X87	Uterovaginal prolapse	-	3.6
4	GI / Liver disease	5.9	D72	Viral hepatitis	-	0.4
			D97	Cirrhosis / liver disease NOS	-	0.9
			D75	Malignant neoplasm colon/rectum	-	1.8
			D85	Duodenal ulcer	365	1.2
			D86	Peptic ulcer other	365	0.9
			D94	Chronic enteritis/ulcerative colitis	-	1.0
5	Oesophagus disease	5.8	D84	Oesophagus disease	365	5.8
6	Visual impairment	9.7	F83	Retinopathy	-	1.6
			F94	Blindness	-	0.4
			F84	Macular degeneration	-	2.6
			F93	Glaucoma	-	5.5
7	Cataract	13.4	F92	Cataract	-	13.4
8	Hearing impairment	8.8	H84	Presbyacusis	-	5.8
			H85	Acoustic trauma	-	0.4
			H86	Deafness	-	2.8
9	Respiratory problems	5.7	K02	Pressure/tightness of heart	365	1.2
			R02	Shortness of breath/dyspnoea w/o K02	365	2.3
			R81	Pneumonia	365	2.4
10	Angina pectoris	11.2	K74	Angina pectoris	365	11.2
11	Myocardial disease	6.3	K75	Acute myocardial infarction	365	5.7
			K76	Other / chronic ischaemic heart disease	-	0.7
12	Heart failure	5.3	K77	Heart failure	-	5.3
13	Atrial fibrillation/flutter	8.2	K78	Atrial fibrillation/flutter	365	8.2

Deficit	Deficit name	Deficit prev.(%)	ICPC[a]	ICPC-Label	Days[b]	Item prev.(%)
14	Hypertension – uncomplicated	35.8	K86	Hypertension uncomplicated	365	35.8
15	Hypertension – complicated	8.8	K87	Hypertension complicated	-	8.8
16	Dizziness	8.1	A06	Fainting/syncope	365	1.6
			H82	Vertiginous syndrome / labyrinthitis	365	4.6
			K88	Postural hypotension	365	0.4
			N17	Vertigo/dizziness	365	1.7
17	TIA / CVA	8.9	K89	Transient cerebral ischaemia	365	3.9
			K90	Stroke/cerebrovascular accident	-	5.2
18	Vascular disease	8.0	K91	Atherosclerosis	-	1.0
			K92	other PVD	-	3.3
			K93	Pulmonary embolism	365	0.7
			K94	Phlebitis/thrombophlebitis	365	1.1
			K99	Cardiovascular disease other	-	2.7
19	Fracture / Osteoporosis	11.3	A80	Trauma/injury NOS	365	1.1
			L72	Fracture: radius/ulna	365	0.5
			L73	Fracture: tibia/fibula	365	0.5
			L74	Fracture: hand/foot bone	365	0.3
			L75	Fracture: femur	365	0.9
			L76	Fracture: other	365	1.1
			L95	Osteoporosis	-	8.0
20	Arthritis / Osteoarthrosis	7.7	L88	Rheumatoid arthritis / related condition	-	1.7
			L89	Osteoarthrosis of hip	-	3.6
			L91	Osteoarthrosis other / related condition	-	2.7
21	Osteoarthrosis knee	6.2	L90	Osteoarthrosis of knee	-	6.2
22	Neurologic disease	7.1	N86	Multiple sclerosis	-	0.2
			N99	Neurological disease, other	-	0.7
			N99	Migraine	365	0.9
			N87	Parkinsonism, Parkinson's disease	-	1.3
			N88	Epilepsy	-	1.5
			N94	Peripheral neuritis/neuropathy	-	3.0
23	Depression	8.0	P03	Feeling depressed	365	2.0
			P76	Depressive disorder	365	6.1
24	Sleep disturbance	11.5	P06	Sleep disturbance	365	11.5
25	Cognitive impairment	5.6	P20	Memory / concentration / orientation disturbance	365	2.3
			P85	Mental retardation	-	0.1
			P70	Dementia / Alzheimer's disease	-	3.3

Deficit	Deficit name	Deficit prev.(%)	ICPC[a]	ICPC-Label	Days[b]	Item prev.(%)
26	Psychiatric problems/ Substance abuse	5.1	P71	Organic psychosis other	365	0.5
			P72	Schizophrenia	-	0.1
			P73	Affective psychosis	365	0.4
			P74	Anxiety disorder/anxiety state	365	1.5
			P15	Chronic alcohol abuse	-	1.6
			P16	Acute alcohol abuse	365	0.1
			P17	Tobacco abuse	-	1.1
			P18	Medication abuse	365	0
			P19	Drug abuse	365	0
27	COPD	8.8	R91	Chronic bronchitis / bronchiectasis	-	0.7
			R95	Chronic obstructive pulmonary disease	-	8.1
28	Asthma	5.8	R96	Asthma	-	5.8
29	Skin problems	6.8	S70	Herpes zoster	365	1.5
			S91	Psoriasis	-	1.7
			S97	Chronic ulcer skin	365	3.7
30	Weight problems	4.9	T05	Feeding problem of adult	365	0.1
			T07	Weight gain	365	0.1
			T08	Weight loss	365	1.3
			T83	Overweight	-	0.8
			T82	Obesity	-	2.7
31	Thyroid disorders	6.2	T85	Hyperthyroidism/thyrotoxicosis	365	1.2
			T86	Hypothyroidism/myxoedema	365	5.0
32	Diabetes mellitus	18.8	T90	Diabetes mellitus	-	18.8
33	Urinary disease	7.5	U99	Urinary disease, other	-	7.5
34	Prostate problems	5.4	Y77	Malignant neoplasm prostate	-	2.1
			Y85	Benign prostatic hypertrophy	-	3.3
35	Social problems	5.7	Z01	Poverty/financial problem	365	0.1
			Z03	Housing/neighbourhood problem	365	0.4
			Z04	Social cultural problem	365	0.2
			Z29	Social problem NOS	365	0.4
			Z12	Relationship problem with partner	365	0.5
			Z14	Partner illness problem	365	1.0
			Z15	Loss/death of partner problem	-	3.4
36	Polypharmacy	28.8	-	-	365	28.8

[a] Dutch ICPC-1 version as currently used in general practices. [b] '365 days' indicates that the belonging item is only considered present when registered at least once in the past year. For items without the '365 days' indication, all time presence is considered. The reported item prevalences on which the Frailty Index deficit arrangement has been based come from this study´s primary care centre, but are based on EMR data of November 2008. prev. = prevalence.

Chapter 6

The effectiveness of a proactive patient-centred primary care program on daily functioning of frail older patients: a cluster randomised controlled trial

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In revision

Abstract

Background

Primary care for frail older people is reported to be suboptimal. A transition toward proactive patient-centred care is needed. We investigated the effectiveness of U-PRIM, a frailty screening intervention based on routine care data, and of U-PRIM followed by U-CARE, a nurse-led personalised care intervention, on daily functioning of frail older people in primary care.

Methods

A single-blind, three-armed, cluster-randomised controlled trial including 3092 older patients recruited from 39 general practices was conducted between October 2010 and March 2012, including one-year follow-up. The general practices were randomly assigned to the U-PRIM, U-PRIM + U-CARE, or control groups. The primary outcome of the study was daily functioning measured on the Katz-15 ADL/IADL scale. The secondary outcomes were quality of life (RAND-36), EuroQol (EQ5-D), primary care consultations, hospital admissions, emergency department visits, nursing home admissions and mortality. Analysis was by intention to treat. This trial is registered as NTR2288.

Results

Patients in both intervention groups demonstrated better preservation of daily functioning than those in the control group at 12 months (mean Katz-15 (95% confidence interval): U-PRIM 1·87 (1·77-1·97), U-PRIM+U-CARE 1·88 (1·80-1·96), and control group 2·03 (1·92-2·13); p = 0·03). In pre-specified subgroup analyses, higher educational level positively affected outcomes for patients in the U-PRIM+U-CARE group. No overall differences in quality of life were observed. The patients in the U-PRIM+U-CARE intervention group consulted their general practice more often by telephone compared to patients in the other groups.

Conclusions

A frailty screening intervention (U-PRIM) and U-PRIM followed by a nurse-led personalised care intervention (U-CARE) led to better preservation of daily functioning compared to the control group. More highly educated older people had additional benefits from U-CARE, indicating that the effect is dependent on individual patient characteristics. Further refinement is necessary to optimise the U-CARE intervention to a heterogeneous group of frail older people.

Background

Providing optimal care for the increasing number of frail older people with complex care needs is a major challenge in primary care.[1] The current approach is reactive and does not meet the needs of older patients, resulting in unnecessary loss of daily functioning, suboptimal quality of life and high health care expenditures.[2,3] Patient-centred medicine has been proposed as a model for transforming primary care.[4] Key components of this transformation include the identification of at-risk patients, followed by longitudinal personalised care. Operationalization of these key components in daily practice is still debated, and their effectiveness, both integrated and in isolation, also remains to be determined.[5]

To identify older patients at risk, numerous instruments have been developed.[6] The Frailty Index (FI), based on health deficits, adequately predicts adverse health outcomes in community-dwelling older people and correlates well with other frailty measures.[7,8] The FI may be easily implemented in primary care when applied to routine patient data.[5]

Although several comprehensive care models for frail older people have been developed, the benefits are controversial.[9,10] Comparison of care models is difficult due to the heterogeneity of intervention components and inclusion criteria. A multidisciplinary approach, individual assessments and tailored care are consistently reported as key elements of such models.[9]

In the Utrecht Proactive Frailty Intervention Trial (U-PROFIT), we designed and evaluated a strategy for proactive patient-centred primary care of frail older people.[11] The strategy consists of the Utrecht Periodic Risk Identification and Monitoring (U-PRIM) system, a frailty screening intervention based on administrative patient data, and U-CARE, a nurse-led personalised care intervention comprising frailty screening, comprehensive geriatric assessment and evidence-based care planning. In a three-armed cluster-randomised trial, we evaluated the effectiveness of U-PRIM and U-PRIM followed by U-CARE on the preservation of daily functioning of frail older people in primary care compared with usual care. Since the intervention was aimed at general practice level, we opted for a cluster-randomised design to prevent contamination between the comparison groups.

Methods

Study design

We conducted a single-blind, three-armed, cluster-randomised controlled trial with one-year follow-up. A detailed study protocol has been described elsewhere.[11] Out of 44 invited general practices in the Utrecht region, the Netherlands, 39 agreed to

participate. Together, these practices provide primary health care for 44·000 patients aged ≥ 60 years. From October 2010 to March 2011, potentially frail patients aged ≥ 60 years were identified by screening their Electronic Medical Records (EMRs) using the U-PRIM criteria (see U-PRIM intervention). Terminally ill patients and patients in assisted-living facilities or nursing homes were excluded. Eligible patients were approached by their GP. Written informed consent was obtained. The U-PROFIT trial was approved by the Institutional Review Board of the University Medical Centre Utrecht (protocol ID 10-149/O).

Randomisation and masking

The participating general practices were stratified according to practice size (small: <1·000; average: 1·000-3·000; large: >3·000 patients). The practices were randomised using a computer-generated random allocation sequence aiming for an allocation ratio at individual participant level of 1:1:1 (Figure 1). We used a modified informed consent procedure, i.e., patients were not aware of the intervention arm they were allocated to and were only fully informed at the end of the study.[12] General practices were instructed not to inform the patients concerning the study aim. Investigators were not blinded for logistic reasons.

Intervention 1: Frailty screening and monitoring intervention using U-PRIM

The U-PRIM intervention aimed to identify potentially frail older patients using readily available routine care EMRs data. Patients aged ≥ 60 years were considered potentially frail if they fulfilled one or more of the following criteria: multimorbidity, polypharmacy or a 'consultation gap'. To measure multimorbidity, we constructed a FI consisting of 50 potential health deficits, each defined as the presence of one or more International Classification of Primary Care (ICPC) coded symptoms or diseases in the patient's EMR. FI scores were defined as the proportion of deficits present with multimorbidity deemed for FI scores > 0·20.[8] Polypharmacy was defined as chronic use of ≥ five different pharmacotherapeutics according to the Anatomic Therapeutic Chemical (ATC) coding.[13] "Consultation gap", defined as at least three years without general practice consultation (except for annual influenza vaccination) was included to detect possible 'care avoiders'.[14]

A quarterly U-PRIM report was generated in the general practice (see appendix 1). U-PRIM group GPs were advised to act upon these reports according to current standards and guidelines.[15]

Intervention 2: U-PRIM followed by a nurse-led personalised care intervention (U-CARE)

In the second arm, U-PRIM selection was followed by U-CARE, delivered by specially trained registered practice nurses. Details of U-CARE were described elsewhere.[16] Briefly, the U-CARE intervention starts with an individual frailty assessment using the Groningen Frailty Indicator (GFI) questionnaire and the Intermed Self-Assessment scale, an instrument that assesses the bio-psychosocial care needs of older patients.[17,18] For patients who were frail according to the GFI questionnaire, nurses conducted a Comprehensive Geriatric Assessment (CGA) as a basis for tailored care, guided by specially developed evidence-based care plans. Twenty-one registered nurses were trained during a six-week training program (total 48 hours). All components were pretested in a pilot study for feasibility and acceptability.

Control group

In the control group, U-PRIM screening was conducted every three months, but results were not visible to the general practices. GPs in the control group were instructed to provide care as usual.

Outcome measurements

All outcomes were assessed at individual patient level, with data collected through questionnaires and EMR data extraction at baseline, six, and 12 months. The modified Katz-15 index ADL/IADL (scale 0-15) was used as primary outcome instead of the Katz-6 index (protocol deviation) as the Katz-6 has a considerable floor effect at low disability levels.[19-21]A higher score indicates a higher ADL/IADL dependency. Secondary outcomes were physical, mental, social and vitality health-related quality of life measured by the RAND-36, EuroQol (EQ-5D), and perceived quality of life score (0-10), satisfaction with primary care (0-10), the number of hospital admissions (protocol deviation, post-hoc analysis), admissions to a nursing home or assisted-living facility; and primary care out-of-hours consultations during follow-up.[22,23] Informal caregiver burden was specified in the study protocol as a secondary outcome, but will be addressed in a separate paper. The following secondary outcomes were collected from the EMR data: the number of emergency department (ED) visits, primary care consultations (by telephone, in surgery or home visits) during office hours; and mortality.

Quality control checks, such as checks for missing data and screening procedures to identify impossible values, were performed for the questionnaires and the EMR data. EMR data was collected and linked by the infrastructure of the Foundation Mondriaan Health Research Data (see appendix 5).

Statistical analysis

A modified intention to treat analysis was performed to detect differences between the intervention groups and the control group. Patient characteristics were reported as means (SD), medians (IQR) or n (%) where applicable. Primary and secondary outcomes after 6 and 12 months follow-up were analysed with generalised linear mixed models. A random intercept was included in all models to account for cluster randomisation. An unstructured residual (i.e., GEE type) covariance matrix was included to correct for the associations between the 6- and 12-month outcomes.[24] Linear mixed models for continuous outcomes were applied for the Katz-15 and the dimensions of the RAND-36, the EQ5D, quality of care, and perceived quality of life. As all outcomes displayed skewed distributions, effects were estimated with robust standard errors. Group means with 95% CIs were estimated from the analysis. Number of nursing home admissions, hospital admissions, general practice consultations within office hours, general practice after-hours consultations and ED visits were analysed as counts and rates with 95% CIs were estimated. Mortality was analysed with logistic mixed models, adjusted probabilities with 95% CIs were estimated. The analyses were performed in three steps. First, a crude model with treatment and time of measurement was estimated. In the second model, we adjusted for baseline values. Third, we adjusted for known confounders including age, gender, socioeconomic status (SES), educational level, indications for inclusion (FI score, polypharmacy and consultation gap) and stratification factor. As the effects of treatment on the outcome may be delayed, we tested the interaction between the interventions and time of measurement. Interactions were tested between outcome measurements and predefined parameters (i.e. age, gender, SES and educational level). When this interaction was significant after correction for confounders and indication, subgroup analyses were performed. P=< 0·05 was considered statistically significant. We corrected for multiple testing with the Holm method.[25] Statistical analyses were performed using SAS version 9·2 (SAS Institute Inc., Cary, North Carolina) and SPSS (IBM, Chicago, IL, USA) version 20·0.

A valid estimation of the variance of the Katz-15 results within and between general practices is not available for the elderly population, and a state-of-the-art power analysis for the cluster-randomised trial was not possible. We initially assumed that with an inclusion of 5000 frail older people, significant effects could be observed in the primary outcome between the three groups. The trial is registered as NTR2288.

Role of the funding source

The sponsors approved the study design but were not involved in the data collection, analysis and interpretation or in writing of the report. The authors had full access to all data as well as the final responsibility for the submission of the manuscript.

Results

Four practices withdrew shortly after randomisation because of technical EMR problems (Figure 1). In the remaining 35 practices, 8156 patients were identified as potentially frail by U-PRIM, 518 were excluded, resulting in 7638 eligible patients. In total, 3092 out of 7638 patients (40·5%) participated (Table 1). Responders did not differ from non-responders with respect to age, sex, FI score, medication use, or length of the consultation gap. Out of 1327 patients in the U-PRIM + U-CARE group, 835 (62·9%) were frail according to the GFI.

Figure 1. Flowchart of general practices and patients assigned to the intervention and control groups

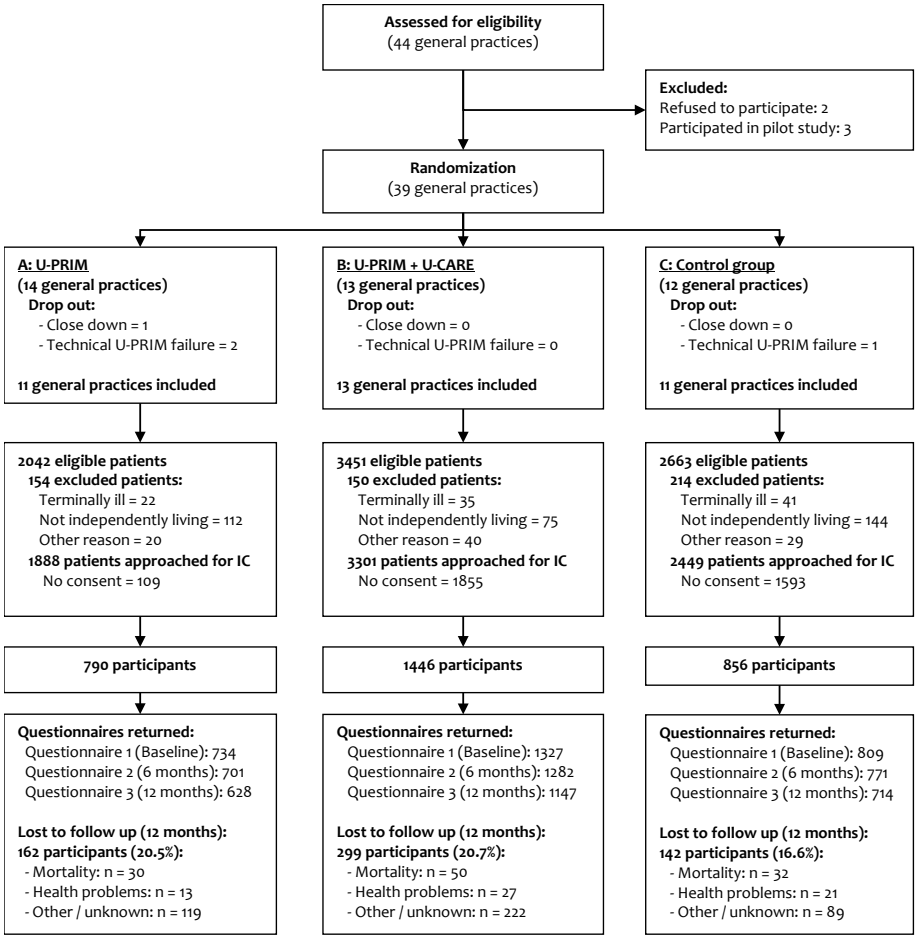

Table 1. Baseline characteristics of general practices and patients

General practice characteristics at baseline		U-PRIM N = 11	U-PRIM + U-CARE N = 13	Control group N = 11
General practice size				
Median cluster size (IQR)		37 (22-92)	62 (33-129)	71 (42-121)
Small (< 1000)		5	7	5
Average (1000-3000)		2	3	3
Large (>3000)		4	3	3
FTE per practice, mean (SD)		1·9 (1·1)	2·7 (1·7)	2·9 (1·3)
Patient characteristics at baseline	**No· of patients with non-missing data**	**U-PRIM N = 790**	**U-PRIM + U-CARE N = 1446**	**Control group N = 856**
Age, mean (SD)	2870	73·5 (8·2)	74 (8·2)	74·6 (8·8)
Female gender, n (%)	2968	406 (55·3)	772 (58·2)	453 (56·0)
Living independently alone, n (%)	2794	226 (31·7)	379 (29·3)	229 (29·1)
Married / living together, n (%)	2847	411 (56·4)	766 (58·2)	465 (58·0)
Having children, n (%)	2731	595 (85·0)	1079 (85·5)	627 (81·5)
Native Dutch, n (%)	2846	669 (91·8)	1223 (93·1)	757 (94·3)
Education				
Low	-	288 (39.5)	529 (40.2)	210 (26.2)
Moderate	-	335 (46.0)	589 (44.8)	364 (45.4)
High	-	106 (14.5)	198 (14.3)	228 (28.4)
SES score				
Low	-	403 (55)	535 (40.4)	139 (17.2)
Moderate	-	224 (30.6)	536 (42)	295 (36.5)
High	-	106 (14.5)	234 (17.7)	374 (46.3)

Katz-15 score, mean (SD)	2858	1·60 (2·29)	1·73 (2·22)	1·74 (2·36)
EQ-5D-NL score, mean (SD)	2870	0·75 (0·23)	0·73 (0·24)	0·75 (0·22)
Self-reported QoL (0-10), mean (SD)	2988	7·2 (1·3)	7·1 (1·3)	7·2 (1·3)
RAND-36 Physical Domain, mean (SD)	2867	58·9 (29·6)	56·8 (29·4)	59·8 (30·0)
RAND-36 Mental Domain, mean (SD)	2869	68·5 (19·5)	69·2 (19·1)	71·6 (17·9)
RAND-36 Social Domain, mean (SD)	2823	43·8 (10·8)	42·8 (11·5)	43·5 (10·2)
RAND-36 Vitality Domain, mean (SD)	2868	55·7 (20·6)	55·6 (20·2)	57·5 (19·3)
Number of diseases in year before inclusion, median (IQR)	2870	2 (1-3)	2 (1-3)	2 (1-3)
Hearing problems, n (%)	2870	226 (30·8)	449 (33·8)	259 (32·0)
Vision problems, n (%)	2870	172 (23·4)	361 (27·2)	232 (28·7)
FI-score, median (IQR)	2687	0·06 (0·02-0·10)	0·08 (0·04-0·10)	0·08 (0·06-0·12)
Medications in chronic use during last year, median (IQR)	2687	6 (5-8)	7 (5-8)	6 (5-8)
Consultation gap, days, median (IQR)	2687	29 (13-64)	35 (21-64)	23 (10-50)
Patients with hospital admissions in previous year, n (%)	2827	168 (23·2)	338 (25·9)	193 (24·2)
Patients in nursing home in previous year, n(%)	2840	6 (0·8)	16 (1·2)	6 (0·7)
Patients with home care, n (%)	2832	184 (25·4)	376 (28·8)	194 (24·2)

EQ5D-NL = EuroQol-5D questionnaire, Dutch version, FI = frailty index, FTE = full-time equivalent, IQR = interquartile range, QoL = quality of life, SD = standard deviation, Education level low: primary school or less, moderate: secondary school, high: more than secondary school. SES = socioeconomic status based on ZIP code. RAND-36: Short Form 36 questionnaire. Percentages represent valid percentages.

Primary outcome

After six months, mean Katz-15 scores of patients among the three groups did not differ significantly (mean score (95% CI): U-PRIM = 1·69 (1·61- 1·77), U-PRIM+U-CARE = 1·70 (1·60- 1·79), control group: 1·74 (1·67- 1·82)). After 12 months, patients of both intervention groups demonstrated better preservation of daily functioning compared to control patients (mean Katz score (95% CI): U-PRIM = 1·87 (1·77-1·97), U-PRIM+U-CARE = 1·88 (1·80- 1·96), control group = 2·03 (1·92-2·13), p = 0·03 time*treatment (Table 2). The ICC value for the Katz-15 corrected for time was 0·031 (95 CI 0·01-0·05). More highly educated patients in the U-PRIM + U-CARE group displayed significantly better preservation of daily functioning compared to their U-PRIM and control group counterparts. Patients in the U-PRIM group with high SES levels reported better preservation of functioning compared to their counterparts in the other groups

Secondary outcomes

At six and at 12 months, no differences were observed between the three groups with respect to the RAND-36 or the EQ-5D (Table 3). Patients in both intervention groups reported better perceived quality of life at 12 months compared with the control group. Patients in the U-PRIM+U-CARE group were (non-significantly) more satisfied with care they received. During one-year follow-up, patients in the U-PRIM+U-CARE group consulted their general practice more frequently by telephone than patients in the other groups (Table 4). More in-practice consultations and home visits was observed in this group. No overall differences in hospital admissions, ED visits or mortality rates were observed. Multivariate analysis for nursing home admissions (n = 32) and admissions to an assisted-living facility (n = 62) was not possible due to the low number of events.

Table 2. Estimated means (95% CI) of physical functioning on the Katz-15 and pre-specified subgroups at 6 and 12 months[a]

	6-Months follow-up			12-Months follow-up			
	U-PRIM Mean (95%CI)	U-PRIM + U-CARE Mean (95%CI)	Control group Mean (95%CI)	U-PRIM Mean (95%CI)	U-PRIM + U-CARE Mean (95%CI)	Control group Mean (95%CI)	p-value
Katz 15	1·69 (1·61- 1·78)	1·70 (1·59- 1·80)	1·75 (1·67- 1·82)	1·87 (1·76- 1·97)	1·88 (1·80- 1·96)	2·03 (1·93- 2·13)	0·03[b]
Katz 15							0·13
Male	1·11 (0·99-1·25)	1·03 (0·91-1·25)	1·00 (0·89-1·11)	1·24 (1·07-1·40)	1·22 (1·09-1·34)	1·36 (1·16-1·56)	0·03[b]
Female	2·17 (2·02-2·31)	2·24 (2·14-2·35)	2·35 (2·22-2·47)	2·39 (2·26-2·52)	2·45 (2·35-2·52)	2·57 (2·48-2·66)	0·09[c]
Katz 15							0·85
Age – 60-74	1·16 (1·06-1·26)	1·09 (0·99-1·20)	1·18 (1·11-1·25)	1·26 (1·15-1·37)	1·22 (1·13-1·31)	1·38 (1·29-1·48)	0·12[c]
Age – 75+	2·28 (2·14-2·42)	2·35 (2·22-2·49)	2·38 (2·24-2·52)	2·56 (2·38-2·74)	2·62 (2·50-2·73)	2·77 (2·55-2·99)	0·36[b]
Katz 15							0·04
SES – low	1·97 (1·85-2·09)	1·92 (1·83-2·02)	1·71 (1·54-1·88)	2·22 (2·08- 2·37)	2·13 (2·04- 2·23)	1·89 (1·61- 2·17)	0·06[c]
SES– moderate	1·62 (1·53-1·71)	1·65 (1·50-1·80)	1·78 (1·65-1·90)	1·75 (1·57- 1·92)	1·77 (1·63- 1·92)	2·18 (1·94- 2·41)	0·008[b]
SES – high	1·57 (1·39-1·78)	1·39 (1·28-1·49)	1·48 (1·40-1·55)	1·55 (1·29- 1·81)	1·70 (1·55- 1·86)	1·69 (1·55- 1·83)	0·003[b]
Katz 15							0·003
Educ. level – low	2·25 (2·11-2·39)	2·22 (2·11-2·33)	2·47 (2·29-2·65)	2·50 (2·31-2·69)	2·46 (2·34- 2·58)	2·71 (2·51- 2·91)	0·03[c]
Educ. level – moderate	1·54 (1·44-1·63)	1·65 (1·51-1·79)	1·60 (1·47-1·73)	1·68 (1·54-1·81)	1·82 (1·70- 1·93)	1·78 (1·63- 1·93	0·20[c]
Educ. level – high	1·14 (0·98- 1·31)	0·91 (0·78-1·05)	0·88 (0·79-0·98)	1·26 (1·04- 1·47)	1·01 (0·83- 1·18)	1·40 (1·19- 1·61)	0·0001[b]

[a] Adjusted for baseline, age, sex, social economic status (SES), education, frailty-index, polypharmacy, consultation gap and practice size. The highest significant level of p-values is reported; [b] p-value for interaction of intervention with time; [c] p-value for intervention.

Table 3. Estimated means (95% CI) of Quality of life and satisfaction of care, 6 and 12 months[a]

	6-Months follow-up			12-Months follow-up				
	U-PRIM Mean (95%CI)	U-PRIM + U-CARE Mean (95%CI)	Control group Mean (95%CI)	U-PRIM Mean (95%CI)	U-PRIM + U-CARE Mean (95%CI)	Control group Mean (95%CI)	p-value	Corrected p-value[h]
RAND-36 Physical[b]	59·50 (58·50- 60·49)	59·45 (58·59- 60·31)	58·37 (57·38- 59·37)	57·15 (55·47- 58·83)	58·32 (57·34- 59·30)	56·61 (55·14- 58·08)	0·13[f]	0.50
RAND 36 social[b]	42·50 (41·68-43·31)	43·03 (42·30- 43·76)	42·58 (41·61- 43·55)	42·46 (41·57- 43·35)	42·66 (42·07- 43·24)	42·29 (41·66- 42·92)	0·54[f]	1.00
RAND 36 mental[b]	70·69 (69·83- 71·55)	70·24 (69·43- 71·05)	69·89 (69·04- 70·75)	68·86 (67·71- 70·02)	69·72 (68·99- 70·44)	68·33 (67·46- 69·21)	0·11[g]	0.50
RAND 36 vitality[b]	56·74 (55·52- 57·95)	56·72 (55·80- 57·64)	56·58 (55·52- 57·63)	56·34 (55·35- 57·34)	55·99 (55·09- 56·90)	54·98 (53·70- 56·26)	0·10[g]	0.50
EQ-5D[c]	0·75 (0·74- 0·76)	0·75 (0·74- 0·76)	0·75 (0·74- 0·76)	0·74 (0·72- 0·75)	0·74 (0·73- 0·75)	0·74 (0·72- 0·75)	0·54[g]	1.00
QoL mark 0-10[d]	7·22 (7·14- 7·30)	7·21 (7·15- 7·28)	7·17 (7·11- 7·23)	7·19 (7·10- 7·29)	7·19 (7·12- 7·26)	7·08 (7·01- 7·16)	0·02[f]	0.14
Satisfaction care[e]	7·88 (7·76- 8·00)	8·05 (7·98- 8·11)	8·02 (7·95- 8·09)	7·84 (7·72- 7·96)	7·98 (7·90- 8·05)	7·91 (7·79- 8·04)	0·048[f]	0.29

[a] Adjusted for baseline, age, sex, social economic status (SES), education, frailty-index, polypharmacy, consultation gap and practice size. [b] RAND-36 all domains: scores range from 0-100. [c] EQ-5D score range from -1 to 1. [d] Quality of life mark between 0-10, higher score indicates higher quality of life. [e] Satisfaction with care received from general practice, score 0-10, higher score, more satisfied. The highest significant level of p-values is reported: [f] p-value for intervention; [g] p-value for interaction of intervention with time. [h] Corrected p-value for multiple testing using Holm correction.

Table 4. Health care consumption and mortality mean rates (95%CI) after 12-months follow-up

	U-PRIM Mean rate (95%CI)	U-PRIM + U-CARE Mean rate (95%CI)	Control group Mean rate (95%CI)	p-value	Corrected p-value[c]
Consultations in general practice and home visits[a]	7·02 (6·20-7·94)	9·34 (8·17-10·68)	7·12 (6·00-8·46)	0·002	0.01
Telephone consultations with general practice[a]	2·76 (2·16-3·51)	4·27 (3·71-4·91)	2·66 (2·01-3·53)	0·0002	0.001
General practice out-of-hours consultation[a]	0·77 (0·63- 0·95)	0·96 (0·78- 1·19)	0·98 (0·81- 1·17)	0·18	0.72
Number hospital admission[a]	0·29 (0·25-0·35)	0·27 (0·24-0·31)	0·33 (0·29-0·39)	0·26	0.78
Emergency department visits[b]	0·12 (0·07-0·18)	0·10 (0·07-0·15)	0·14 (0·10-0·21)	0·49	0.98
Mortality, adjusted for age	0·002 (0- 0·01)	0·003 (0-0·01)	0·004 (0·001- 0·2)	0·70	0.98

[a] Adjusted for baseline, age, sex, education, SES, frailty index, polypharmacy, consultation gap and practice size. [b] Adjusted for age, sex, education, SES, frailty index, polypharmacy, consultation gap and practice size. [c] Corrected p-value for multiple testing using Holm correction.

Discussion

In this large-scale cluster-randomised trial, U-PRIM and U-PRIM + U-CARE resulted in better preservation of daily functioning in older patients compared with usual care after one-year follow-up. Additional benefits of U-PRIM + U-CARE could not be demonstrated in the overall comparison, but were observed in preservation of daily functioning of more highly educated patients. No overall differences in quality of life were observed. Patients in the U-PRIM+U-CARE group consulted their general practice more often than patients of the other groups.

The benefits of the U-PRIM on the Katz-15 were small indicating a limited effect of screening only. Among more highly educated patients, the benefit of U-PRIM remained in the same range (0·14 points), whereas the benefits of the combined U-PRIM + U-CARE intervention nearly tripled (0·39 points). This difference indicates that the effectiveness of U-CARE is related to individual patient characteristics. Educational level is associated with health-related and psychosocial factors in older people, defining patients' individual needs.[26,27] Older persons report that a sense of acknowledgement by their healthcare providers and a good relationship are prerequisites for patient-centred care.[28] Understanding the individual needs of patients is crucial. This suggests that the U-CARE intervention requires refinement to optimally meet the diverse needs of frail older persons. The effects on the Katz-15 scale in SES subgroups are less clear, which might be due to the measurement of SES at community level with postal codes. No differences in quality of life measured with the RAND-36 were observed. Difficulties in measuring quality of life in older people are reported: Even persons with substantial health problems may still report good quality of life.[29] The fact that patients in the U-PRIM+U-CARE group consulted their general practice more often than those in the other groups is not surprising, given the timely detection of health problems and increased efforts by the nurse.

Our study has several limitations. We did not monitor detailed actions of the GPs in the U-PRIM group during follow-up. In addition, application of and adherence to different U-CARE intervention components were difficult to monitor given the personalised nature of U-CARE. The effect size may have been relatively small due to short follow-up period. However, given a trend of increasing effect over time, treatment effects may be more pronounced after longer follow-up. Adequate implementation of a complex intervention may require time to achieve sufficient benefits. Multiple secondary outcomes were assessed which increases the risk of false-positive findings. Therefore, we applied the Holm correction, resulting in adjusted p-values with limited reduction of statistical power.[25] Of eligible patients, 41% participated. Although responders did not differ from

non-responders in most aspects, selective inclusion cannot be ruled out. Furthermore, the sample-size of 5000 patients proved unattainable. This target was based on a highly speculative scenario where we hypothesised a difference of 0·2 between the U-PRIM and control group and 0·5 between the UPRIM+U-CARE and control group after 12 months. With a significance level of 5% and 90 % power, a cluster size of 60 patients and an ICC of 0·05, this resulted in a sample size of 4788. The significance of the findings is largely influenced by the correction for confounders. In particular, the baseline measurements of the outcome reduced the sample size needed, a phenomenon well described in the methodological literature.[30] Additionally, the number of participants differ among groups due to dropout, difficulties in U-PRIM implementation, variability in practice size of the 'large' stratified practice group and differences in consent rates (42%, 44% and 35% in the U-PRIM, U-PRIM + U-CARE and control group respectively). Given the modified informed consent procedure, these differences cannot be explained by knowledge of group assignment. Some GPs reported that patients with known cognitive disorders were not explicitly detected by the U-PRIM, suggesting that cognitive disorders might have been underestimated by U-PRIM or under-registered by the GPs. Moreover, only 62·9% of patients in the U-PRIM + U-CARE group were frail according to the GFI and continued to receive U-CARE. This probably led to an underestimation of the true effect because we analysed the total intervention group. Because we did not collect GFI data in the U-PRIM and control groups, we could not compare the treatment effect on GFI positive patients. Patients who experienced difficulties filling out questionnaires were assisted by practice nurses or research assistants, which could have led to a limited amount of bias. Finally, no possible side effects arising from the extra proactive care provided to frail older patients were addressed.

The current study is unique in its robust design and magnitude. The U-PROFIT trial is, to our knowledge, the largest cluster-randomised trial evaluating a multicomponent intervention in frail older people embedded in routine primary care. A single-blind design was used with a modified informed consent procedure to reduce selection bias and dropout in the control group. In the design, recruitment and evaluation, we followed the recommendations for studies on preventing disability in older persons.[31] Mixed models analyses were performed, not only to correct for cluster effects but also to evaluate potential time effects during follow-up. By adhering to the guidelines for the performance of subgroup analyses, we provided a solid basis for the interpretation of our subgroup results. Nevertheless, our findings for treatment effects for subgroups should be interpreted with caution and evaluated to provide further evidence.[32] We

used an age threshold of 60, to include non-Dutch-origin patients in whom frailty is reported to start earlier. We hypothesised that the intervention might have a different effect on the 'oldest old'; however, no such effect was observed. A frailty instrument was used based on existing primary care EMR patient data which included criteria associated with adverse events and other frailty measures.[7,8] This appealing approach can easily be implemented in routine care. In contrast, a performance-based measure such as the frailty phenotype,[33] would demand extra time and staff, which was not feasible. In the U-PRIM+U-CARE group, a two-step screening approach using U-PRIM, including FI, and GFI, was employed; thus two complementary, easy-to-use frailty instruments provide valuable starting points for patient-centred care.

In conclusion, screening of older patients for frailty using routine primary care data (U-PRIM) and U-PRIM followed by nurse-led care intervention (U-CARE) lead to better preservation of daily functioning compared to care as usual. Subgroup analysis revealed that more highly educated older patients perceived additional benefits from this nurse-led intervention, suggesting that its effectiveness depends on individual patient characteristics. Further refinement is needed to optimally address the individual needs of frail older people.

Panel: Research in context

Systematic review

In a systematic review and meta-analysis, Beswick et al. concluded that complex interventions can help older persons safely live independently, although the frailest patients seem to benefit the least.[9] To assess whether the combined and independent effectiveness of both intervention components has been established since 2008, we searched PubMed for relevant cluster randomised trials with the terms 'frailty', 'screening and monitoring', and 'comprehensive geriatric assessment' in combination with the terms 'personalised care' or 'patient-centered care' and 'primary care' and their synonyms in any heading between January 2008 and March 2013. No three-armed cluster randomised trials were found that evaluated the effectiveness of both interventions separately and combined, and no studies identified patients based on existing GP patient record data. Four two-armed trials were published that met our criteria. An advanced-practice nurse in-home health consultation program for community-dwelling older persons aged 80 years or older showed a reduction in adverse health outcomes but did not demonstrate an improvement in quality of life.[34] 'Guided-Care', a nurse-led intervention to enhance quality of health care for multimorbid older people, showed improvements on self-reported quality of chronic health care and

reduced use of home care but had little effect on the use of other health services.[10] Van Hout et al. reported that a preventive home visiting program did not demonstrate any beneficial effects on physical functioning or health care utilisation.[35]

Interpretation

The current study is the first that investigated the effectiveness of the frailty identification instrument based on existing patient data and this instrument followed by a multicomponent nurse-led care intervention. This study adds support to the use of existing patient data to detect frail older persons in primary care. More research is needed to assess the optimal type and intensity of treatment in this heterogeneous group of older people. We hypothesise that when health problems are detected in an earlier phase, a reduction in adverse events (e.g. ED-visits, hospital admissions) will be achieved after a longer follow-up period.[36] Future studies should consider this finding in designing research in this area.

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Appendix 1. Lay-out of U-PRIM report

Patient	Sex	Age	FI score	Multimorbidity	Polypharmacy	Care gap
Smith	F	87	0,26	13	12	5
Jones	M	63	0,22	11	16	18
Taylor	F	70	0,20	11	8	3
Brown	F	75	0,20	10	10	77
Smith	M	81	0,16	8	5	330
Johnson	F	72	0,14	7	6	32
White	F	94	0,08	5	4	1503

Appendix 2. Estimated means (95% CI) of daily functioning, Quality of life and satisfaction of care 6 and 12 months, crude analyses, adjusted for baseline, and adjusted for all confounders

	6-Months follow-up			12-Months follow-up				
	U-PRIM Mean (95%CI)	U-PRIM+ U-CARE Mean (95%CI)	Control group Mean (95%CI)	U-PRIM Mean (95%CI)	U-PRIM + U-CARE Mean (95%CI)	Control group Mean (95%CI)	p-value	Adjusted p-value[h]
Katz15								
Crude	1·65	1·91	1·73	1·81	2·12	1·97	0·22[g]	-
	(1·37- 1·91)	(1·73- 2·09)	(1·48- 1·98)	(1·49- 2·12)	(1·93- 2·31)	(1·71- 2·23)	0·46[f]	
Adjusted for	1·71	1·74	1·73	1·87	1·92	1·98	0·60[g]	-
baseline	(1·62- 1·81)	(1·65- 1·83)	(1·65- 1·79)	(1·66- 1·80)	(1·86- 1·99)	(1·87- 2·08)	0·25[f]	
Adjusted for	1·69	1·70	1·75	1·87	1·88	2·03	0·18[g]	-
Confounders[a]	(1·61- 1·78)	(1·59- 1·80)	(1·67- 1·82)	(1·76- 1·97)	(1·80- 1·96)	(1·93- 2·13)	0·03[f]	
RAND 36 physical[b]								
Crude*	59·55	56·28	59·99	57·42	55·12	58·85	0·18[g]	1.00
	(56·04- 63·06)	(53·79- 58·77)	(56·34- 63·64)	(53·63- 61·20)	(52·73- 57·52)	(55·13- 62·57)	0·33[f]	
Adjusted for	59·25	58·90	58·49	57·01	57·76	57·23	0·81[g]	1.00
Baseline	(58·09- 60·41)	(58·30- 59·51)	(57·34- 59·64)	(55·48- 58·54)	(56·902 58·60)	(55·53- 58·94)	0·25[f]	
Adjusted for	59·50	59·45	58·37	57·15	58·32	56·61	0·13[g]	1.00
Confounders[a]	(58·50- 60·49)	(58·59- 60·31)	(57·38- 59·37)	(55·47- 58·83)	(57·34- 59·30)	(55·14- 58·08)	0·19[f]	

	6-Months follow-up			12-Months follow-up				
	U-PRIM Mean (95%CI)	U-PRIM+ U-CARE Mean (95%CI)	Control group Mean (95%CI)	U-PRIM Mean (95%CI)	U-PRIM + U-CARE Mean (95%CI)	Control group Mean (95%CI)	p-value	Adjusted p-value[h]
RAND 36 social[b]								
Crude	42·83	42·79	43·11	43·10	42·29	42·83	0·63[g]	1.00
	(42·01- 43·64)	(42·10- 43·49)	(42·13- 44·10)	(42·12- 44·09)	(41·42- 43·17)	(42·07-43·59)	0·49[f]	
Adjusted for	42·69	43·00	43·14	42·82	42·53	42·87	0·86[g]	1.00
baseline	(41·89- 43·49)	(42·32- 43·68)	(42·19- 44·08)	(41·87- 43·78)	(41·80- 43·25)	(42·12- 43·62)	0·65[f]	
	42·50	43·03	42·58	42·46	42·66	42·29	0·54[g]	1.00
Adjusted for	(41·68-43·31)	(42·30- 43·76)	(41·61- 43·55)	(41·57- 43·35)	(42·07- 43·24)	(41·66- 42·92)	0·87[f]	
Confounders[a]								
RAND 36 mental[b]								
Crude	69·64	68·73	71·56	67·96	68·33	70·50	0·10[g]	1.00
	(67·63- 71·64)	(67·72- 69·74)	(69·55- 73·56)	(65·88- 70·05)	(66·82- 69·84)	(68·52- 72·48)	0·15[f]	
Adjusted for	70·47	69·76	70·27	68·82	69·38	69·04	0·99[g]	1.00
baseline	(69·28- 71·65)	(69·09- 70·44)	(69·46- 71·07)	(67·48- 70·15)	(68·67- 70·09)	(68·04- 70·04)	0·12[f]	
Adjusted for	70·69	70·24	69·89	68·86	69·72	68·33	0·17[g]	1.00
confounders[a]	(69·83- 71·55)	(69·43- 71·05)	(69·04- 70·75)	(67·71- 70·02)	(68·99- 70·44)	(67·46- 69·21)	0·11[f]	
RAND 36 vitality[b]								
Crude	56·19	55·21	57·79	55·87	54·73	56·63	0·30[g]	1.00
	(54·04- 58·34)	(53·78- 56·63)	(55·29- 60·30)	(53·89- 57·86)	(52·91- 56·56)	(54·22- 59·04)	0·24[f]	
Adjusted for	56·61	56·29	56·84	56·36	55·79	55·57	0·83[g]	1.00
baseline	(55·24- 57·97)	(55·54- 57·05)	(55·70- 57·97)	(55·16- 57·56)	(54·95- 56·64)	(54·46- 56·67)	0·11[f]	
Adjusted for	56·74	56·72	56·58	56·34	55·99	54·98	0·62[g]	1.00
confounders[a]	(55·52- 57·95)	(55·80- 57·64)	(55·52- 57·63)	(55·35- 57·34)	(55·09- 56·90)	(53·70- 56·26)	0·10[f]	

	6-Months follow-up			12-Months follow-up				
	U-PRIM Mean (95%CI)	U-PRIM+ U-CARE Mean (95%CI)	Control group Mean (95%CI)	U-PRIM Mean (95%CI)	U-PRIM + U-CARE Mean (95%CI)	Control group Mean (95%CI)	p-value	Adjusted p-value[h]
EQ5-D[c]								
Crude	0·75	0·72	0·76	0·74	0·72	0·75	0·10[g]	1.00
	(0·73- 0·77)	(0·70- 0·75)	(0·74- 0·79)	(0·71- 0·76)	(0·70- 0·74)	(0·73- 0·77)	0·59[f]	
Adjusted for	0·75	0·74	0·75	0·73	0·74	0·74	0·54[g]	1.00
baseline	(0·73- 0·76)	(0·74- 0·75)	(0·74- 0·76)	(0·72- 0·75)	(0·73- 0·75)	(0·73- 0·75)	0·61[f]	
Adjusted for	0·75	0·75	0·75	0·73	0·74	0·73	0·95[g]	1.00
confounders[a]	(0·74- 0·76)	(0·74- 0·75)	(0·74- 0·76)	(0·72- 0·75)	(0·73- 0·75)	(0·72- 0·75)	0·54[f]	
QoL mark 0-10[d]								
Crude	7·20	7·13	7·23	7·21	7·11	7·16	0·44[g]	1.00
	(7·07- 7·34)	(7·05- 7·22)	(7·10- 7·36)	(7·07- 7·34)	(7·03- 7·20)	(7·02- 7·29)	0·38[f]	
Adjusted for	7·22	7·21	7·20	7·21	7·18	7·12	0·64[g]	1.00
baseline	(7·11- 7·32)	(7·15- 7·26)	(7·14- 7·26)	(7·10- 7·33)	(7·12- 7·20)	(7·04- 7·21)	0·39[f]	
Adjusted for	7·22	7·21	7·17	7·19	7·19	7·08	0·02[g]	0.86
confounders[a]	(7·14- 7·30)	(7·15- 7·28)	(7·11- 7·23)	(7·10- 7·29)	(7·12- 7·26)	(7·01- 7·16)	0·54[f]	
Satisfaction care[e]								
Crude	7·86	8·07	7·95	7·83	8·01	7·87	0·22[g]	1.00
	(7·64- 8·07)	(7·93- 8·20)	(7·80- 8·01)	(7·79- 8·04)	(7·88- 8·15)	(7·69- 8·05)	0·80[f]	
Adjusted for	7·90	8·02	7·98	7·87	7·98	7·90	0·15[g]	1.00
baseline	(7·77- 8·01)	(7·96- 8·09)	(7·89- 8·07)	(7·75- 7·99)	(7·90- 8·06)	(7·79- 8·01)	0·69[f]	
Adjusted for	7·88	8·05	8·02	7·84	7·98	7·91	0·048[g]	1.00
confounders[a]	(7·76- 8·00)	(7·98- 8·11)	(7·95- 8·09)	(7·72- 7·96)	(7·90- 8·05)	(7·79- 8·04)	0·62[f]	

[a] Adjusted for baseline, age, gender, social economic status (SES), education, frailty-index, polypharmacy consultation gap and practice size. [b] RAND-36 all domains: scores range from 0-100. [c] EQ5D score range from -1 to 1. [d] Quality of life mark: scores range between 0-10. Higher scores indicate higher quality of life. [e] Satisfaction care general practice: scores range from 0-10. Higher scores indicate more satisfaction. The highest significant level of p-values is reported: [f] p-value for interaction of intervention with time; [g] p-value for intervention. [h] Corrected p-value for multiple testing using Holm correction.

Appendix 3. Health care consumption mean rates and prevalence (95%CI) after 12-months follow-up, crude and adjusted for confounders

	U-PRIM Mean rate (95%CI)	U-PRIM + U-CARE Mean rate (95%CI)	Control group Mean rate (95%CI)	p-value	Corrected p-value[c]
Consultations and home visits in general practice					
Crude	5·86 (4·51-7·60)	8·30 (7·05-9·77)	7·72 (6·25-9·54)	0·07	0·28
Adjusted[a]	7·02 (6·20-7·94)	9·34 (8·17-10·68)	7·12 (6·00-8·46)	0·002	0·01
Telephone consultations, practice nurse or doctor's assistant					
Crude	2·27 (1·69-3·04)	4·17 (3·39-5·13)	2·81 (2·12-3·71)	0·0002	0·001
Adjusted[a]	2·76 (2·16-3·51)	4·27 (3·71-4·91)	2·66 (2·01-3·53)	0·005	0·02
General practice out-of-hours consultation					
Crude	0·89 (0·72- 1·10)	1·03 (0·86- 1·23)	1·02 (0·84- 1·23)	0·55	1·00
Adjusted[a]	0·95 (0·80- 1·11)	1·30 (1·15- 1·45)	1·12 (0·90- 1·34)	0·004	0·02
Number hospital admission					
Crude (score 0-5)	0·26 (0·23-0·31)	0·25 (0·22-0·29)	0·30 (0·26-0·36)	0·21	0·63
Adjusted[a]	0·29 (0·25-0·35)	0·27 (0·24-0·31)	0·33 (0·29-0·39)	0·17	0·51
Emergency department visits					
Crude	0·13 (0·09- 0·18)	0·13 (0·10- 0·18)	0·16 (0·11- 0·23)	0·72	1·00
Adjusted[b]	0·12 (0·07-0·18)	0·10 (0·07-0·15)	0·14 (0·10-0·21)	0·49	0·98
Mortality					
Crude	0·008 (0- 0·02)	0·007 (0- 0·02)	0·02 (0·01- 0·04)	0·04	0·20
Adjusted[c]	0·002 (0- 0·01)	0·003 (0-0·01)	0·004 (0·001- 0·2)	0·70	0·98

[a] Adjusted for baseline, age, sex, education, SES, frailty index, polypharmacy, consultation gap and practice size. [b] Adjusted for age, sex, education, SES, frailty index, polypharmacy, consultation gap and practice size . [c] Adjusted for age. [d] Corrected p-value for multiple testing using Holm correction.

Appendix 4. Subgroup analyses, estimated means and rates (95%CI) at 12 months

	U-PRIM Mean (95% CI)	U-PRIM + U-CARE Mean (95% CI)	Control group Mean (95% CI)	p-value	Corrected p-value[f]
EQ5D[a]				0·0495[c]	0·09
Age – 60-74	0·77 (0·75- 0·78)	0·77 (0·75- 0·78)	0·76 (0·75- 0·78)	0·54[e]	
Age – 75+	0·70 (0·68- 0·72)	0·71 (0·70- 0·73)	0·71 (0·69- 0·73)	0·40[d]	
RAND-36 physical[a]				0·004[c]	0·02
Education level – low	49·82 (48·75- 50·90)	47·10 (44·69- 49·52)	48·43 (46·62- 50·25)	0·54[e]	
Education level – moderate	58·97 (57·70- 60·24)	59·28 (57·25- 61·30)	58·93 (57·47- 60·39)	0·39[d]	
Education level – high	68·28 (65·14- 71·43)	73·16 (71·54- 74·79)	70·57 (66·83- 74·30)	0·01[d]	
Self-reported QoL (0-10)[a]				0·03[c]	0·09
Male	7·32 (7·17- 7·47)	7·32 (7·19- 7·46)	7·16 (7·00- 7·32)	0·02[d]	
Female	7·10 (6·92- 7·29)	7·08 (6·97- 7·20)	7·03 (6·87- 7·20)	0·67[e]	
General practice out-of-hours consultations[b]				0·002[c]	0·01
Education level – low	1·04 (0·73- 1·48)	1·09 (0·87- 1·36)	1·01 (0·64- 1·59)	0·95[e]	
Education level– moderate	0·86 (0·62- 0·94)	0·86 (0·74- 1·00)	1·22 (0·94- 1·60)	0·02[e]	
Education level – high	0·60 (0·37-0·97)	0·92 (0·62 1·35)	0·53 (0·31- 0·91)	0·19[e]	
General practice out-of-hours consultations[b]				0·24[c]	0·24
SES – low	0·72 (0·49- 1·05)	1·07 (0·73- 1·58)	1·23 (0·65- 1·95)	0·13[e]	
SES – moderate	0·88 (0·60- 1·27)	0·77 (0·48- 1·22)	0·83 (0·53- 1·30)	0·88[e]	
SES – high	0·50 (0·30- 0·83)	0·83 (0·64- 1·07)	0·77 (0·56- 1·08)	0·19[e]	

	U-PRIM Mean (95% CI)	U-PRIM + U-CARE Mean (95% CI)	Control group Mean (95% CI)	p-value	Corrected p-value[f]
Emergency department visits[b]				0·02[c]	0·08
Education level – low	0·14 (0·09-0·23)	0·08 (0·06- 0·12)	0·11 (0·06- 0·18)	0·23[e]	
Education level – moderate	0·06 (0·03- 0·11)	0·10 (0·07- 0·14)	0·13 (0·07- 0·24)	0·21[e]	
Education level – high	0·10 (0·04- 0·23)	0·05 (0·03- 0·12)	0·06 (0·03- 0·15)	0·51[e]	
Telephone consultations with general practice[b]				0·001[c]	0·008
Education level – low	2·68 (2·04-3·53)	4·62 (4·07-5·26)	2·85 (2·16-3·77)	0·0003[e]	
Education level – moderate	1·96 (1·49-2·58)	4·19 (3·50-5·02)	2·46 (1·92-3·16)	<0·0001[e]	
Education level – high	2·78 (2·14-3·60)	3·35 (2·58-4·35)	1·72 (1·37-2·16)	0·0003[e]	
Consultation and visits with general practice[b]				0·01[c]	0·05
Education level – low	8·27 (7·21- 9·49)	10·06 (9·17- 11·04)	7·81 (6·51- 9·35)	0·01[e]	
Education level – moderate	6·51 (5·65- 7·49)	9·16 (8·03- 10·45)	7·23 (5·99- 8·73)	0·002[e]	
Education level – high	6·79 (5·36- 8·59)	7·43 (6·19- 8·91)	6·44 (5·16- 8·03)	0·63[e]	

[a] Adjusted for baseline, age, sex, education, SES, frailty index, polypharmacy, consultation gap and practice size. [b] Adjusted for age, sex, education, SES, frailty index, polypharmacy, consultation gap and practice size. [c] P-value for interaction test of variable with intervention in overall model. Within the subgroup analyses, the highest significant level of p-values is reported: [d] p-value for interaction of intervention with time; [e] p-value for intervention. [f] Corrected p-value for multiple testing using Holm correction.

Appendix 5. The Mondriaan Foundation

The Mondriaan Foundation is an independent organisation which aims to link and enrich routine health care databases in the Netherlands for (pharmaco-)epidemiological research. Data sources are linked through a trusted third party (TTP) using privacy enhancing technology. All data requests are conditional on approval by an independent scientific advisory committee and the obligation to make results publicly available.

Appendix 6. Post-hoc power calculation

When designing this trial, we considered several scenarios, both with and without correction for clustering. In one scenario, we hypothesised a difference of 0.2 between the U-PRIM and control group and 0.5 between the U-PRIM + U-CARE and control group after 12 months. With a significance level of 5% and 90% power, this yielded 404 patients per arm. We assumed a cluster size of 60 patients and an ICC of 0.05, which increased the sample size needed to 4,788 or 1,596 patients per arm. Given the fact that all values used for this calculation were highly speculative, we specifically chose not to construct a sample size based on speculative data but instead to explain this both in the submitted manuscript as well as the protocol paper. Furthermore, we did not include both repeated measurements and correction for the primary outcome at baseline. With a response rate of 41%, we included > 3000 patients. The significance of our findings is largely influenced by the correction for known confounders. In particular, the baseline measurements of the outcome reduced the sample size needed, a phenomenon well described in the methodological literature.[1] However, the observed effect was lower than the effect provided in the scenario when designing the trial. To illustrate the point of baseline correction further, we performed sample size calculations for the presented outcomes after twelve months with proc power in SAS, a procedure that allows for sample size calculation with (and without) correction for known confounders (without cluster correction). In a scenario where correction for baseline was not included, the sample size required for a significance level of 0.05 with a power of 0.80 would have been 12,504. However, after correction for baseline Katz-15, this sample size was reduced to 170 patients, largely due to the high correlation of 0.83 between the Katz-15 at baseline and after 12 months.

References

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Chapter 7

Economic evaluation of a proactive patient-centered primary care program for frail older patients: cost-effectiveness analysis alongside the U-PROFIT randomised controlled trial

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Abstract

Objective

An economic evaluation of a proactive, patient-centered primary care program for frail older people compared with usual primary care.

Design

Cost-effectiveness analysis from a societal perspective embedded in a single blind, three-armed, cluster-randomised controlled trial with 12 months follow-up.

Participants

A total of 3092 potentially frail patients aged 60 years and older, living independently.

Setting

Thirty-nine general practices in the Netherlands.

Interventions

U-PRIM, a frailty screening intervention based on routine care data, and U-PRIM followed by U-CARE, a nurse-led personalized care intervention.

Main outcome measures

The primary outcome measure was incremental costs per quality adjusted life year (QALY) gained.

Results

The total costs per patient were €6 651 (± 14 686 SD) for U-PRIM, €6 825 (± 11 452 SD) for U-PRIM + U-CARE and € 7 601 (± 15 717) for usual care. At a willingness-to-pay of € 20 000 per QALY, there was a 36% chance that U-PRIM was cost-effective and a 75% chance that U-PRIM + U-CARE was cost-effective compared with usual care.

Conclusions

A frailty screening intervention (U-PRIM) followed by a nurse-led proactive personalized care program (U-CARE) has a high probability of being cost-effective compared with usual care. Combined with the findings from our associated clinical trial, in which we demonstrate the preservation of older patients' level of daily functioning, we recommend implementation of the U-PRIM + U-CARE intervention for proactive primary care for frail, community-dwelling older people.

Trial Registration

The Dutch Trial Registry, NTR2288.

Background

Worldwide, the number of people aged 60 years and older will rise from 600 million in 2000 to 2 billion in 2050.[1] A substantial number of these older people will experience frailty, i.e., an increased risk of adverse health outcomes.[2] Frail older people often have multiple chronic diseases and limitations in their Activities of Daily Living (ADL).[3,4] With their resulting complex care needs, the elderly population places a large burden on healthcare resources.[5,6] In the United States, total healthcare expenditures for people aged 65 were $ 368.1 billion in 2008, which was almost one-third of the total healthcare budget.[7] For people with five or more chronic diseases, healthcare spending is fourteen times higher than for people without any chronic disease.[8] In the Netherlands, € 28 billion (37.6%) of the total healthcare budget of € 74 billion was spent on care for people aged 65 years and older.[9] Because healthcare costs for older people place a major burden on society, the efficient delivery of care is important to ensure as many positive health effects as possible for the money invested.

Most care needs of older people are addressed in primary care. As gatekeepers to the healthcare system, General Practitioners (GPs) resolve more than 90% of the health problems in the overall population.[10] Based on the integrated, patient-centered approach and the long-lasting relationship with their patients, GPs have a key role in the provision and coordination of care for frail older patients.[11,12] However, at present, the care for older people in general practice is reactive and fragmented, and the care needs of frail older people are not adequately met.[11,13-15] A paradigm shift is needed from reactive care, in which GPs respond to individual emerging health problems, to a more proactive, population-based care provision.[15,16]

The current evidence for the cost-effectiveness of proactive primary care for older people is scarce and difficult to compare across studies.[17,18] We designed and implemented a strategy for proactive primary health care for older people (U-PROFIT) consisting of the systematic identification of frail older people (U-PRIM) and a subsequent nurse-led, proactive and personalized care program (U-CARE) and demonstrated its effectiveness in delaying functional decline in the elderly population.[19,20] The aim of the present study is to evaluate the cost-effectiveness of the U-PROFIT strategy and its separate components.

Methods

Design cost-effectiveness study

We performed an incremental cost-effectiveness analysis from a societal perspective comparing the two interventions for proactive care for frail older people as evaluated in the U-PROFIT trial, with usual care as the control condition. We evaluated the costs and effects at 12 months, which is the full follow-up period of the U-PROFIT trial.

The U-PROFIT trial

Design clinical trial

The economic evaluation was performed using data collected during the U-PROFIT trial, which has been described elsewhere in detail.[19,20] In brief, we conducted a single blind, three-armed, cluster- randomised controlled trial in 39 general practices in the Utrecht region of the Netherlands that provide primary healthcare to approximately 44 000 patients aged 60 years and older. In this trial, we evaluated the effectiveness of the frailty screening program (U-PRIM) and that of U-PRIM followed by a nurse-led proactive care program (U-CARE) on the level of daily functioning of frail, community-dwelling older patients compared with the usual primary care. Because the intervention was targeted at the level of the general practice, we chose a cluster-randomized design to prevent contamination.

Interventions

The U-PRIM intervention consisted of a software application that identifies patients at risk for frailty by screening routine electronic medical record (EMR) data from these general practices. Patients aged 60 years and older were considered potentially frail and included in a quarterly U-PRIM report when they met at least one of the following criteria: multimorbidity (frailty index ≥ 0.20), polypharmacy (≥ five medications in chronic use) or a consultation gap (at least three years without general practice consultation except for the annual influenza vaccination).[19,21-23] In the U-PRIM group, GPs were asked to use the reports in proactive care and to conform to current professional guidelines.[24] In the U-PRIM + U-CARE group, the U-PRIM report was followed by the U-CARE intervention. U-CARE consisted of a detailed individual frailty assessment followed by a Comprehensive Geriatric Assessment (CGA) at home and evidence-based tailored care for those patients who were frail according to the initial assessment.[25] To provide the U-CARE intervention, 21 registered nurses were trained in a six-week program (48 hours of training). In the control group, GPs and other primary care providers were asked to continue their usual care provision.

Participants

Within the participating general practices, we approached 7638 eligible patients, i.e., patients aged 60 years and older who met at least one of the U-PRIM selection criteria. In total, 3092 patients (40.5%) provided written informed consent.

Data collection and resource valuation

Intervention costs

The costs of the U-PRIM and U-PRIM + U-CARE interventions were calculated using a bottom-up approach (see appendix A). In brief, we collected information on the time dedicated to the interventions by the GPs and practice nurses and the related costs based on their hourly honoraria. Information on costs of U-PRIM start-up and maintenance, the U-CARE educational program for the practice nurses, and the U-CARE toolkit and website (two instruments used by the practice nurses in the U-CARE program) was collected alongside the development and implementation of the interventions. Next, we calculated the number of potentially frail older people per general practice, assuming a standard Dutch practice size of 2350 patients.[26] In a standard general practice, on average, 552 patients (23.5%) are 60 years and older.[27] Within this older population, 110 patients (20%) would be selected as potentially frail in the U-PRIM report.[20] With these data, we calculated all intervention costs per average-sized general practice and converted them to 'costs per potentially frail older patient per year'.

Healthcare utilization costs and informal care costs

At 12 months, we extracted EMR data on daytime GP consultations and Emergency Department (ED) visits. With questionnaires at 12 months, we collected data on the following measures of health care utilization among participating older people: the number of out-of-hours GP consultations, hospital admissions, permanent and temporary nursing home admissions and permanent and temporary residences in assisted living facilities, home care and day care.[19] The questionnaire adopted the full follow-up period of 12 months as a recall period. With questionnaires at baseline, 6 months, and 12 months directed at the patients' informal caregivers, we gathered data on how many hours per week patients received informal care. In each questionnaire, the informal caregivers were asked to report on the week before they received the questionnaire. We used the Dutch Manual for cost research in healthcare to value the healthcare resources and provision of informal care in terms of their unit costs (Table 1).[28] We indexed prices to the level of 2012.[29]

Effect measures

In the questionnaires at baseline, 6 months, and 12 months, we collected data on the patients' health status using the three-level EuroQoL EQ-5D.[30] We applied the Dutch EQ-5D tariff to calculate mean utility values for the different health states derived from the EQ-5D responses.[31]

Statistical analysis

We performed all analyses based on an intention to treat principle. Using five factors (age, sex, marital status, frailty index, and self-rated health) to predict the missing values, we employed multiple imputations to account for missing data in the healthcare utilization measures and the EQ-5D.[32-34] Next, we calculated the total costs for each patient by multiplying the healthcare resources used by the respective unit costs. In addition, we calculated the QALYs for each patient using an area under the curve approach with linear interpolation of the EQ-5D utility values among the baseline, 6-month, and 12-month data.[35] Missing EQ-5D utility values for patients known to be deceased were set at zero. The U-PRIM + U-CARE intervention group had a slightly lower value for the baseline EQ-5D. To avoid bias in the QALY calculation, we corrected for imbalances in the baseline EQ-5D utility values using a regression-based approach.[36] Using the mean total costs and effects for each intervention group, we divided the incremental costs by the difference in QALY to obtain the incremental cost-effectiveness ratios (ICER) for U-PRIM and U-PRIM + U-CARE compared with usual care and for U-PRIM + U-CARE compared with U-PRIM.[37] This base case analysis was performed from a societal perspective, i.e., including all assessed costs in the imputed data set with the adjusted QALYs. To estimate the uncertainty around the ICERs, we used bootstrapping with 1000 iterations. With these bootstrapped cost-effect pairs, we constructed cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs) alongside a spectrum of different amounts society would be willing to pay for one QALY. As a reference value, amounts between € 20 000 and € 80 000 are being used in the Netherlands. As is common for this type of intervention, we adopted a willingness-to-pay (WTP) of € 20 000.[38]

To examine the robustness of our results, we planned a number of sensitivity analyses: first, a sensitivity analysis from the healthcare perspective, i.e., excluding the costs related to the provision of informal care; second, a sensitivity analysis on complete cases only; and third, a sensitivity analysis using QALYs unadjusted for baseline EQ-5D imbalances. Furthermore, we performed a subgroup analysis based on age, dividing the study population into patients aged 60 to 74 years and patients aged 75 years and older.

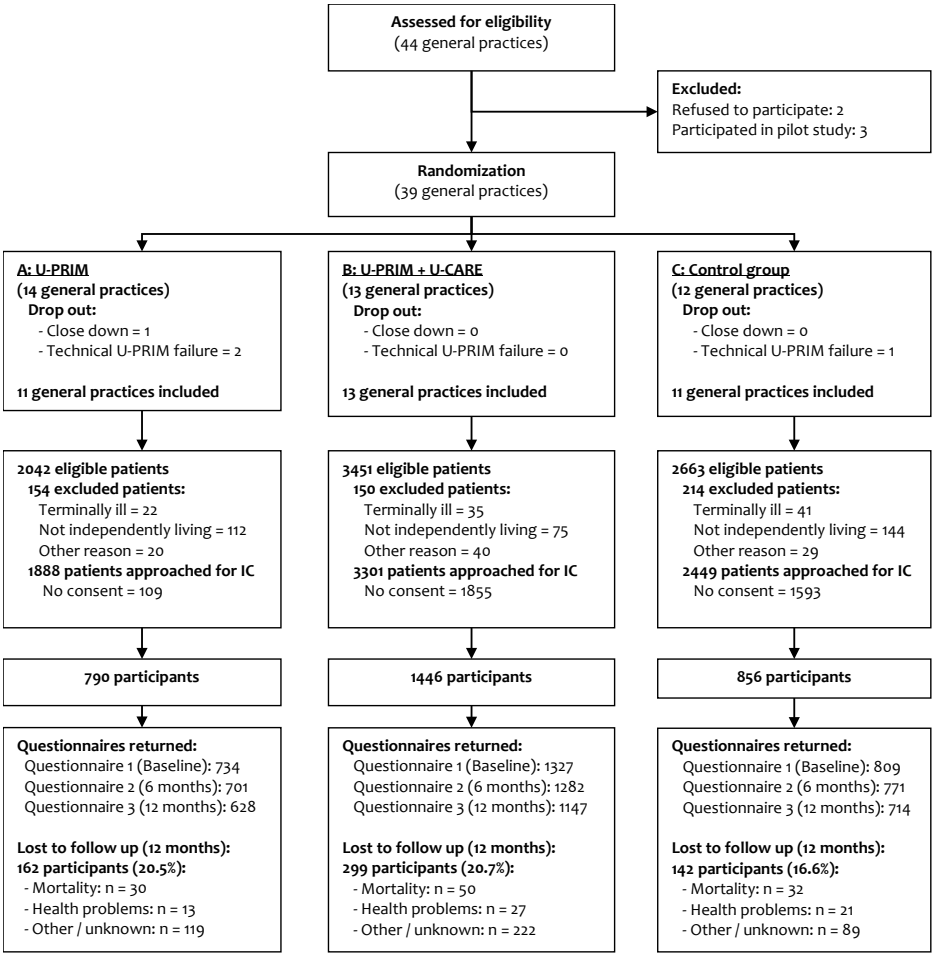
Results

Characteristics of the study population

The inclusion process and baseline characteristics of our study population have been described in detail elsewhere.[20] In brief, out of 3092 patients, 790 patients received the U-PRIM intervention, 1446 patients received the U-PRIM + U-CARE intervention, and 856 patients received the usual care (Figure 1). The mean age of the study population was 73.5 years (± 8.2 SD), and 55.3% was female. In total, 427 patients (13.8%) had an informal caregiver who was willing to participate in the trial by answering the questionnaires targeted at informal care provision. In the U-PRIM, U-PRIM + U-CARE and usual care groups, 162 (20.5%), 299 (20.7%) and 142 (16.6%) patients, respectively, did not complete the 12-month follow-up.

In total, 10.4% of the EQ-5D data was missing, with 2508 patients (81.1%) having complete EQ-5D data available. For the healthcare utilization measures, 16.8% of the data was missing, with 2063 patients (66.7%) having complete data available. When considering the total of 427 informal caregivers, data related to the hours of provided care were missing for 14.6% of the provided informal care, with 278 informal caregivers (65.1%) having complete data available.

Figure 1. Flowchart of general practices and patients assigned to the intervention and control groups



Healthcare utilization, costs and effects

Patients in the U-PRIM group had fewer GP in-surgery consultations or home visits than patients in the other two groups, whereas patients in the U-PRIM + U-CARE group had the highest rate of GP consultations by telephone (Table 1). Furthermore, patients in the U-PRIM + U-CARE group spent notably fewer days in a nursing home than patients in the other two groups. There was also a trend for fewer days in the hospital for both intervention groups.

Patients in the U-PRIM and U-PRIM + U-CARE groups had healthcare utilization costs that were lower by € 693 and € 815 over the 12-month period, respectively, than patients in the usual care group (Table 2). When considering costs related to the hours of informal care provided, patients in the U-PRIM and U-PRIM + U-CARE groups had expenses that were € 285 and € 92 lower, respectively, than that of the usual care group. With intervention costs of € 28 for the U-PRIM group and € 131 for the U-PRIM + U-CARE group included, the mean total costs in the intervention groups were lower than that in the usual care group (mean costs per patient in € (± SD) per group: U-PRIM: 6651 (14 686); U-PRIM + U-CARE: 6825 (11 452); Usual care: 7601 (15 717)). Without adjustment for baseline EQ-5D imbalances, patients in the U-PRIM + U-CARE group had the lowest QALYs. After correction for the baseline EQ-5D figures, patients in this group had slightly higher QALYs than the patients in the U-PRIM and usual care groups (Table 2). Based on the differences between these point estimates of imputed costs and on imputed and adjusted effects in the single study sample, the ICER of U-PRIM vs. usual care was € 190.000 / QALY, whereas the U-PRIM + U-CARE intervention dominated the usual care.

Cost-effectiveness analyses

Considering the 1000 bootstrapped iterations, the U-PRIM intervention resulted in a cost savings of € 980 (95% CI -245 to 477), a QALY differences of 0.0048 (95% CI -0.0266 to 0.0162), and an ICER of -12 033 compared with usual care (Table 3). Among all the bootstrapped data pairs, 60% were situated in the southwest quadrant of the cost-effectiveness plane, indicating both lower effectiveness and lower costs. The CEAC demonstrated that at a WTP of € 20 000, the probability of cost-effectiveness was 36% (Figure 1a). Because of the low probability that U-PRIM would be cost-effective as a stand-alone intervention, the pre-specified comparison of U-PRIM + U-CARE and U-PRIM was not examined. When the combined U-PRIM + U-CARE intervention was compared with usual care, a cost savings of € 815 (95% CI -2025 to 350) and a QALY gain of 0.0067 (-0.0112 to 0.0243) were generated, resulting in a dominant ICER (Table 4). Evaluating the cost-effectiveness plane, 71% of the bootstrapped data pairs were situated in the

southeast quadrant, indicating higher effectiveness and lower costs, i.e., superiority compared with the usual care group. The probability of cost-effectiveness at a WTP of € 20 000 was 75% (Figure 2).

Sensitivity and subgroup analyses

In the comparison of U-PRIM with usual care, sensitivity analyses revealed no major results that were notably different from the base case analysis. Only in the subgroup analysis of patients aged 75 years and older, the majority of bootstrapped data pairs were was now situated in the northwest quadrant, indicating the inferiority of the U-PRIM intervention (Table 3). This finding resulted in a drop in the probability of being cost-effective at a WTP of € 20 000 from 36% to 14%. When comparing U-PRIM + U-CARE with usual care in the sensitivity analysis with unadjusted QALYs, the bootstrapped data pairs shifted on the cost-effectiveness plane from dominance in the base case analysis to the majority being situated in the southwest quadrant, indicating an effect loss that was compensated for by the cost savings (Table 4). The probability of being cost-effective decreased from 75% to 21%. In the complete case sensitivity analysis, the probability of U-PRIM + U-CARE being cost-effective compared with usual care decreased to 48%.

Table 1. Costs of resource use and utilization in the U-PRIM, U-PRIM + U-CARE, and control groups

Type of utilisation	Costs		Mean (SD) utilisation		
	Unit	Unit cost (€)	U-PRIM n = 790	U-PRIM + U-CARE n = 1446	Control group n = 856
Interventions:					
U-PRIM start up and maintenance expenses	Per patient / year	7.10	1	1	N/A
U-PRIM usage in proactive care (direct patient consultations excluded)	Per patient / year	20.90	1	1	N/A
U-CARE education, toolkit, website	Per patient / year	1.65	N/A	1	N/A
U-CARE program usage in proactive care (direct patients consultations excluded)	Per patient / year	101.30	N/A	1	N/A
Healthcare utilization:					
GP consultations (nr per year)	Per consultation	30.95[a]	7.44 (5.48)	9.62 (6.94)	9.81 (8.38)
GP consultation by telephone (nr per year)	Per consultation	14.90[a]	3.18 (4.14)	4.83 (5.52)	3.53 (4.71)
Out-of-hours GP consultations (nr per year)	Per consultation	98.30[b]	1.02 (1.87)	1.14 (2.21)	1.18 (2.18)
Home care (hours per week)	Per hour	37.20[a]	1.40 (4.36)	1.40 (2.70)	1.54 (5.15)
Nursing home (days per year)	Per day	252.75[a]	2.11 (20.15)	1.13 (8.88)	3.06 (16.59)
Assisted living facility (days per year)	Per day	95.60[a]	1.57 (12.55)	1.34 (10.04)	1.26 (10.19)
Day care (days per week)	Per day	47.80[a]	0.05 (0.40)	0.05 (0.40)	0.03 (0.36)
Emergency Department visits (visits / year)	Per visit	160.35[a]	0.16 (0.46)	0.15 (0.47)	0.17 (0.50)
Hospital admission (days in hospital / year)	Per day	485.30[a]	2.06 (5.92)	2.14 (6.66)	2.38 (5.59)
Informal care:					
Care provided by informal caregiver	Per hour	13.30[a]	2.45 (9.92)	2.73 (11.50)	2.86 (11.70)

Values reflect the imputed data of the study sample. Values are means (SD) unless stated otherwise. All costs are indexed to 2012. [a] According to the Dutch manual for cost studies (Hakkaart-van Roijen, 2011). [b] According to the Dutch Healthcare Authority (www.nza.nl). See appendix 1 for detailed information on the composition of the unit costs of the interventions, healthcare utilization, and informal care provision.

Table 2. Mean total costs and effects of the U-PRIM, U-PRIM + U-CARE, and control groups at the 12-month follow up

	Mean total effects or costs (SD)		
Variable	**U-PRIM**	**U-PRIM + U-CARE**	**Control group**
Costs (€)			
Costs directly related to interventions, mean (SD)	28 (0)	131 (0)	0 (0)
Healthcare utilization costs, mean (SD)	4 928 (11 427)	4 806 (7 512)	5 621 (12 289)
Informal caregiver costs, mean (SD)	1 695 (6 861)	1 888 (7 950)	1 980 (8 092)
Total costs, mean (SD)	6 651 (14 686)	6 825 (11 452)	7 601 (15 717)
Effects			
EQ-5D utility value (complete cases)			
Baseline, mean (SD)	0.742 (0.237)	0.725 (0.244)	0.747 (0.226)
Six months, mean (SD)	0.727 (0.254)	0.712 (0.262)	0.735 (0.256)
Twelve months, mean (SD)	0.707 (0.291)	0.702 (0.275)	0.721 (0.269)
EQ-5D utility value (imputed data)			
Baseline, mean (SD)	0.741 (0.231)	0.724 (0.236)	0.746 (0.221)
Six months, mean (SD)	0.726 (0.246)	0.711 (0.252)	0.731 (0.248)
Twelve months, mean (SD)	0.703 (0.271)	0.699 (0.258)	0.714 (0.257)
QALYs			
Imputed and unadjusted, mean (SD)	0.722 (0.225)	0.710 (0.224)	0.728 (0.223)
Imputed and adjusted, mean (SD)	0.698 (0.217)	0.709 (0.222)	0.703 (0.208)

Table 3. Results of the cost-effectiveness analyses: U-PRIM group compared with the usual care group

Analysis	Δ Cost (€) (95% CI)	Δ Effect (95% CI)	ICER	Distribution (%) cost effectiveness plane (quadrant) North east[a]	South east[b]	South west[c]	North west[d]	Prob. cost-effectiveness at WTP of € 20 000
Base case analysis:								
Societal perspective, adjusted QALYs	-980 (-2545 to 477)	- 0.0048 (-0.0266 to 0.0162)	-12 033	0.01	0.31	0.60	0.07	36%
Sensitivity analyses:								
Healthcare perspective	-651 (-1761 to 455)	- 0.0049 (-0.0253 to 0.0166)	752 545	0.03	0.28	0.59	0.10	37%
Unadjusted QALYs	-491 (-2482 to 435)	-0.0061 (-0.0276 to 0.0159)	251 181	0.01	0.28	0.62	0.09	35%
Complete cases	-2288 (-6185 to 1870)	0.0012 (-0.0219 to 0.0244)	Dominant	0.07	0.47	0.40	0.07	49%
Subgroup analyses:								
60-74 years	-2 168 (-3770 to -438)	- 0.0037 (-0.0315 to 0.0233)	245 329	0.00	0.40	0.60	0.01	41%
75+ years	546 (-1482 to 3710)	- 0.0106 (-0.0426 to 0.0196)	Inferior	0.16	0.09	0.12	0.64	14%

Δ Cost is the mean difference in the costs of 1 000 bootstrapped samples. Δ Effect is the mean difference in the effect of 1000 bootstrapped samples. In the situation of cost savings and effect gain, the ICER is 'dominant'. In the situation of extra expenditures and an effect loss, the ICER is 'inferior'. In the situation of cost savings with an effect loss, or extra expenditures with an effect gain, the ICER is calculated as the mean of 1000 bootstrapped ICERS, with each bootstrapped ICER calculated on an individual cost and effect difference. [a] U-PRIM more effective and more costly than usual care. [b] U-PRIM more effective and less costly than usual care (dominant). [c] U-PRIM less effective and less costly than usual care. [d] U-PRIM less effective and more costly than usual care (inferior).

Table 4. Results of the cost-effectiveness analyses: U-PRIM + U-CARE group compared with the usual care group

Analysis	Δ Cost (€) (95% CI)	Δ Effect (95% CI)	ICER (95% CI)	Distribution (%) cost effectiveness plane (quadrant) North east[a]	South east[b]	South west[c]	North west[d]	Prob. cost-effectiveness at WTP of € 20 000
Base case analysis:								
Societal perspective, adjusted QALYs	-815 (-2025 to 350)	0.0067 (-0.0112 to 0.0243)	Dominant	0.05	0.71	0.20	0.05	75%
Sensitivity analyses:								
Healthcare perspective	-668 (-1671 to 211)	0.0066 (-0.0121 to 0.02614)	Dominant	0.03	0.72	0.20	0.04	75%
Unadjusted QALYs	-413 (-2112 to 366)	-0.0185 (-0.0358 to 0.0009)	83 852	0.00	0.03	0.88	0.09	21%
Complete cases	-2843 (-6335 to 196)	-0.0002 (-0.0202 to 0.0203)	-736 005	0.01	0.47	0.49	0.02	48%
Subgroup analyses:								
60-74 years	-891 (-2474 to 530)	- 0.0003 (-0.0248 to 0.0246)	6 236	0.04	0.45	0.44	0.07	51%
75+ years	-320 (-2423 to 1003)	0.0107 (-0.0150 to 0.0346)	Dominant	0.17	0.63	0.13	0.07	70%

Δ Cost is the mean difference in the costs of 1,000 bootstrapped samples. Δ Effect is the mean difference in the effect of 1000 bootstrapped samples. In the situation of cost savings and an effect gain, the ICER is 'dominant'. In the situation of extra expenditures and an effect loss, the ICER is 'inferior'. In the situation of cost savings with an effect loss, or extra expenditures with an effect gain, the ICER is calculated as the mean of 1000 bootstrapped ICERS, with each bootstrapped ICER calculated on an individual cost and effect difference. [a] U-PRIM + U-CARE more effective and more costly than usual care. [b] U-PRIM + U-CARE more effective and less costly than usual care (dominant). [c] U-PRIM + U-CARE less effective and less costly than usual care. [d] U-PRIM + U-CARE less effective and more costly than usual care (inferior)

Figure 2. Cost-Effectiveness Acceptability Curves (CEACs) showing the probability of cost-effectiveness (y-axis) of U-PRIM and U-PRIM + U-CARE for different willingness-to-pay thresholds (x-axis)

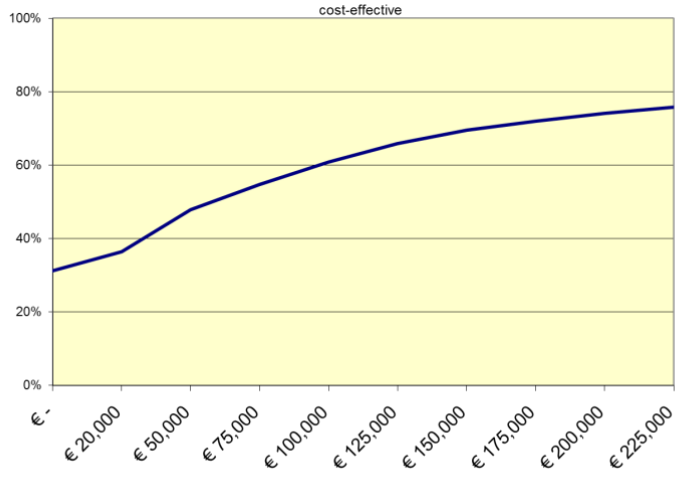


Figure 2a. CEAC for U-PRIM compared with usual care

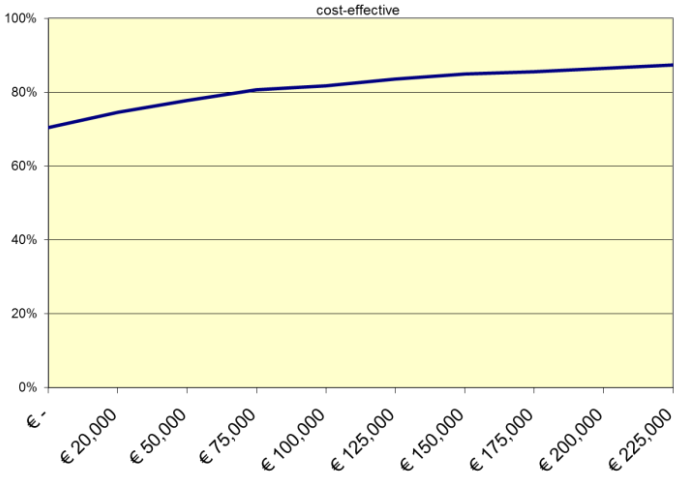


Figure 2b. CEAC for U-PRIM + U-CARE compared with usual care

Discussion

Principal findings

In this cost-effectiveness analysis, we demonstrated that a proactive, patient-centered primary care program consisting of U-PRIM, a frailty screening intervention based on routine care data, followed by U-CARE, a nurse-led personalized care intervention, is cost-effective compared with the usual primary care. At a WTP of € 20 000 per QALY, U-PRIM followed by U-CARE had a 75% probability of being cost-effective compared with usual care. At the same WTP, the U-PRIM intervention alone had a 36% probability of being cost-effective compared with usual care. Given the latter low probability of cost-effectiveness and the corresponding low likelihood of implementing U-PRIM as a stand-alone intervention, we did not perform a cost-effectiveness analysis of U-PRIM + U-CARE compared with U-PRIM alone. In the comparisons of both intervention groups with the usual care group, the effect differences were relatively minor, and the magnitude of the incremental cost-effectiveness ratio was mainly determined by the size of the cost savings.

Limitations and strengths

Our study has some limitations. First, we mainly used self-reported data, which increases the risk of underreporting service use due to recall bias.[39,40] This risk may be aggravated by using questionnaires with a 12-month recall period in a vulnerable population of older people. However, because we applied a modified informed consent procedure in the U-PROFIT trial, patients were unaware of their group assignment.[41] Therefore, we assume that the risk of underreporting is equal among the groups and unlikely to have influenced the ICERs. Second, data were missing from both the healthcare utilization measures and the EQ-5D measures. Because missing data are unlikely to occur randomly, a complete case analysis would lead to biased results, and thus we employed a multiple imputation strategy. In the complete case sensitivity analysis, the probability of cost-effectiveness of U-PRIM + U-CARE compared with usual care declined from 75% to 48%. However, this decline was mainly due to a very minor shift in the QALY difference because the cost savings in the U-PRIM + U-CARE group actually increased substantially. This effect also occurred in the sensitivity analysis with the unadjusted QALYs. Third, to fully assess the effect of the complex interventions on healthcare utilization and QALYs, a longer follow-up period would have been preferable. However, for logistical reasons, such a follow up was not feasible, and there were not enough data available in the literature to consider a modelling approach. Fourth, although we collected a broad range of healthcare utilization data, we did not collect data on a number of healthcare

resources, such as outpatient consultations with a medical specialist and types of medication used. As the U-PRIM and U-CARE interventions were aimed at preventing acute derailments and outpatient specialist consultations are usually scheduled, pre-planned visits, we hypothesize that a short-term significant change in the consultation rate would be unlikely. As we did not find any differences between the intervention groups in the number of medications used (increase in medication use over one year in the U-PRIM, U-PRIM + U-CARE, and usual care groups of 0.6, 0.7, and 0.6, respectively, resulting in the chronic use of 7.5 (± 2.7SD), 7.8 (± 3.0SD), and 7.1 (± 2.7SD) medications at 12 months, assessed in patients selected as potentially frail by U-PRIM), we assume that not taking medication costs into account did not lead to a large risk of biased results. Fifth, the EMR did not distinguish between actions performed by the GP and those by the practice nurses. However, we resolved this issue by using previously published estimates of the time investments of GPs and nurses for the proactive primary care of older people (appendix A). Sixth, we did not correct for other baseline characteristics in the subgroup analysis of age. In the 60-74-year-old age group, 52% were female; in the 75-year-old-and-older age group, 61% were female. Although the cost-effectiveness of U-PRIM + U-CARE compared with usual care appears to be even more distinct in the subgroup of patients aged 75 years or older, the different gender distributions make it difficult to draw an unbiased conclusion. In addition, the apparent higher cost-effectiveness in the older age group could be attributed to a relatively minor increase in effectiveness, whereas the cost savings were still the largest in the youngest age group. Finally, we did not take into account other effect measures. We considered a cost-effectiveness analysis using the Katz-15 index, the questionnaire on the activities of daily living, which was the primary outcome measure in the U-PROFIT trial, as an outcome parameter. However, in the absence of a threshold value for the WTP for one unit of Katz improvement, drawing conclusions with relevance for both policymakers and clinical practitioners would have been difficult.

The current study is unique because it was embedded in a robustly designed, large cluster-randomised controlled trial evaluating the effectiveness of proactive, personalized primary care on the level of daily functioning of frail older people. As the U-PROFIT trial was a pragmatic trial embedded within routine primary care, it closely reflected daily clinical practice, ensuring that the results of this cost-effectiveness analysis have high practical relevance. The results are highly generalizable due to the participation of a large number of diverse general practices. We used the societal perspective, employed a multiple imputation strategy to account for missing data, corrected for baseline imbalances in the EQ-5D, used an accurate bottom-up approach

to calculate the intervention costs and performed various sensitivity analyses to evaluate the robustness of our results. Finally, we considered evaluating both the cost-effectiveness of U-PRIM + U-CARE compared with usual care and with the U-PRIM intervention alone. The latter would have been relevant in the case of a high probability of cost-effectiveness of the U-PRIM intervention as the added value of U-CARE over U-PRIM would have been a major consideration. However, given the low probability of cost-effectiveness of the U-PRIM intervention, the comparison of U-PRIM + U-CARE with U-PRIM was thought to be redundant; therefore, we did not perform that analysis. The comparison of U-PRIM + U-CARE is of high practical relevance because the full strategy would be implemented in a 'usual care' situation, and thus the added value of the combined U-CARE + U-PRIM strategy compared with usual care must be considered.

Implications for research, practice and policy

Our results indicate that the U-PRIM + U-CARE strategy has a high probability of being cost-effective compared with the usual primary care, mainly because of the cost-saving aspect. The cost-effectiveness and clinical effectiveness beyond 12 months are unknown. Because the implementation of complex interventions in daily clinical practice always takes time, we hypothesize that the cost savings and effects will at least consolidate or even increase after 12 months of follow-up. However, further studies are necessary to evaluate this hypothesis.[42] The implementation of U-PRIM as a freestanding intervention would have a low probability of cost-effectiveness, and we therefore do not recommend this implementation. Considering the high probability of cost-effectiveness and the effectiveness in preserving the level of daily functioning, as demonstrated in our clinical trial paper, we currently recommend implementing the U-PRIM + U-CARE intervention for proactive primary care for frail, community-dwelling older people.

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Appendix 1. Determination of the unit costs of the interventions, healthcare utilization and informal care provision

General assumptions used throughout the unit cost calculations

First, in general, we defined the number of potentially frail older people per general practice, assuming a standard Dutch practice size of **2350 patients**.[1] On average, 552 patients (23.5%) in a standard practice are 60 years and older.[2] Within this older population, **110 patients (20%)** were selected as potentially frail in the U-PRIM report.[3] With these data, we converted all calculated intervention costs to the unit 'costs per potentially frail older patient per year'. Second, in all calculations, we applied a VAT tariff of 21%. Third, for a surcharge related to items such as social obligations and vacation bonuses on honoraria defined from collective labour agreements, we apply **39%** for practice nurses, and **35%** for general practitioners.[4] Fourth, for the below-mentioned calculation of the costs directly related to the interventions, we have only taken into account the actions of the GPs and practice nurses not involving direct patient contact as this latter category is already covered in the administration of healthcare utilization. Fifth, all costs mentioned in this appendix have been indexed to 2012.[5]

Unit costs of U-PRIM and U-CARE interventions

U-PRIM start-up and maintenance expenses

Scenarios given by different software development companies (Proigia, http://www.proigia.nl; and Insider, http://www.insider.nl):

	First scenario*	Second scenario**	Mean of two scenarios
One-time installation charges written off over three years, per year	€ 181.50	€ 82.50	€ 132
Maintenance expenses per patient per year¥	€ 0.04	€ 0.40	€ 0.22

¥ Per patient in overall practice population.

Adoption of the mean of the two scenarios:
(132 + 0.22 * 2350) * 1.21 = € 785.29 per standard general practice including VAT.
785.29 / 110 = **€ 7.10 per potentially frail older patient per year for U-PRIM installation charges and maintenance expenses.**

U-PRIM usage in proactive care

Assumption of a time investment of one hour per week for evaluating the total U-PRIM report and preparing proactive care according to current professional guidelines (personal communication of time estimation by Mattijs Numans, professor of general practice). The assumption is that half of this time will be invested by the GP and the remaining half by the practice nurse.

Honorarium practice nurse:[6]

Salary scale 50, step 4 = € 18.54 / hour.

18.54 * 1.39 = € 25.77 / hour.

Honorarium GP:[7,8]

Honorarium derived from tax data: € 45.18 / hour.

Honorarium derived from collective labour agreement, step 4: € 47.73 / hour.

Mean honorarium GP: € 46.46 / hour.

46.46 * 1.35 = € 62.72 / hour.

Taking the mean of the hourly wages of practice nurses and GPs:

(25.77 + 62.77)/2 = € 44.27 / weekly hour of U-PRIM usage in proactive care for all patients in the report.

44.27 * 52 = € 2302.04 / year of U-PRIM usage in proactive care for all patients in the report.

2302.04 / 110 = **€ 20.90 per potentially frail older patient per year for U-PRIM usage in proactive care.**

Total U-PRIM intervention costs: 7.10 + 20.90 = € 28 per potentially frail older patient. This calculation was performed with the exception of direct patient contacts, as these are taken into account within the registered healthcare utilization.

U-CARE education, toolkit, and website.

Education:

Based on the workload and number of potentially frail older patients per standard practice, 0.33 full-time equivalents (fte) of practice nurse per general practice was estimated to be needed for adequate provision of the U-CARE proactive care program.

Costs of delivery of the educational program:
Invoice for 48 hours of education of 21 practice nurses at the school of advanced education: € 5851.
5851 / 21 = € 279 educational costs per practice nurse.
279 / 3 = € 93 educational costs per general practice.
93 / 110 = € 0.85 per potentially frail older patient per year for the education itself.

Costs of time investment of practice nurse in educational program:
Time investment practice nurse = 48 hours.
Hourly honorarium practice nurse = € 25.77 (see calculation 2.2).
48 * 25.77 = € 1236.96 per practice nurse.
1236.96 / 3 = € 412.32 per general practice.
Write off the time investment costs over a period of five years:
0.20 * 412.32 = € 82.46 per general practice per year.
82.46 / 110 = € 0.75 per potentially frail older patient per year for the time investment of practice nurses in the education of the U-CARE program.
0.85 + 0.75 = € 1.60 per potentially frail older patient per year for all items related to U-CARE education.

Toolkit:
Invoice printing office for 500 toolkits: € 2448.60.
2448.60 / 500 = € 4.90 per toolkit.
One practice nurse needs one toolkit, and one general practice needs 0.33 fte practice nurses:
4.90 / 3 = € 1.63 per general practice.
1.63 / 110 = € 0.01 per potentially frail older patient per year for the toolkit.

Website (this website is used by the practice nurse to register patient questionnaire data):
First estimation website developer (www.reinaris.nl): € 0.04 / potentially frail older patient per year.

Total costs for U-CARE education, toolkit and website = 1.60 + 0.01 + 0.04 = € 1.65 per potentially frail older patient per year.

U-CARE program usage in proactive care

The time investments mentioned below are based on estimations of the time investments of GPs and practice nurses for the provision of proactive care for older people, which have been published by a cooperation of insurance companies. [9]

Time investment per year of GPs per potentially frail older patient: 57 minutes. These 57 minutes include consultations of the GP with the practice nurse, multidisciplinary consultations and the preparation of proactive care actions. Actions involving direct patient contact are excluded because they are already taken into account in the healthcare utilisation costs.

Time investment per year of practice nurses per potentially frail older patient: 97 minutes. These 97 minutes include consultations of the practice nurse with the GP, the construction of tailored, personalised care plans, multidisciplinary consultations and administrative tasks. Again, actions involving direct patient contact are excluded because they are already accounted for in the healthcare utilisation costs.

Costs of U-CARE usage in the proactive care by the GP:
Time investment: 57 minutes.
Hourly honorarium: € 62.72 (see 2.2).
(57 * 62.72) / 60 = € 59.58 per potentially frail older patient per year.

Costs of U-CARE usage in the proactive care by the practice nurse:
Time investment: 97 minutes.
Hourly honorarium: € 25.77.
(97 * 25.77) / 60 = € 41.66 per potentially frail older patient per year.

59.58 + 41.66 = € 101.24 for the time investment of GPs and practice nurses for U-CARE per potentially frail older patient per year.

Total intervention costs for the U-PRIM + U-CARE strategy: € 28 + € 1.65 + €101.24 = € 131 per potentially frail older patient. This calculation excludes the costs related to direct patient contacts, as these are included in the healthcare utilization costs.

Unit costs of healthcare utilization

As defined in Table 1 of the main manuscript file, all unit costs were defined according to the Dutch manual for cost studies and indexed to 2012.[4,5] For a number of healthcare utilization types, some additional specifications were made, which are specified in this section.

GP consultations during office hours:

This type of healthcare utilization refers to consultations with the patients' own GPs during office hours, either in surgery or at home.

Unit cost of in-surgery GP consultation: € 29.73.

Unit cost of GP consultation at home: € 45.66.

The mean ratio of in-surgery consultations to consultations at home is 12 to 1.[10]

This calculation results in the following summary measure:

((12 * 29.73) + 45.66) / 13 = € 30.95 per GP consultation.

Out-of-hours GP consultations:

This type of healthcare utilization refers to consultations with GPs during nights or weekend days and can be either in-surgery or at-home consultations.

The unit cost of this type of healthcare utilization was not provided in the Dutch manual for costing studies, and has therefore been taken from another source.[11]

Unit cost of out-of-hours, in-surgery GP consultation: € 90.75.

Unit cost of out-of-hours, at-home GP consultation: € 136.13.

The mean ratio of out-of-hours, in-surgery consultations to at-home consultations is 5 to 1.[12] This calculation results in the following summary measure:

((5 * 90.75) + 136.13) / 6 = € 98.30 per out-of-hours GP consultation.

Chapter 8

Prediction of adverse health outcomes in community-dwelling older people using routine primary care data

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Submitted

Abstract

Background

To facilitate proactive care and tailored decision-making in the increasing number of frail older people, general practitioners (GPs) need to be able to identify patients who are at risk of adverse health outcomes. Based on our previously developed U-PRIM frailty screening instrument, we evaluated prognostic models based on routine Electronic Medical Record (EMR) data to further improve risk assessment in frail older patients, both in a population-based approach and during individual consultations.

Methods

We carried out a prognostic cohort study with a five-year follow-up period in patients aged 60 years and older who attended 21 urban primary care centres. We extracted baseline information on candidate predictors from the GPs' EMRs. The combined main outcome was nursing home admission and death. Three prognostic models were evaluated with Cox regression analysis: the first model included age, sex, polypharmacy, consultation gap, and Frailty Index (FI) score; in the second model, the FI score was replaced by geriatric events, psychosocial events, and multimorbidity; and the third model included all available predictors. From the second model, we derived a prediction rule for use in individual consultations.

Results

A total of 13420 patients (7443 women, mean age 71.0 years, SD 8.6) were included. In total, 2013 patients (15%) experienced an outcome event. With the exception of sex, each predictor was associated with the risk of nursing home admission and death. All three multivariable models showed good discriminatory ability, with the third model demonstrating superior performance (c-statistic 0.781, 95% CI 0.771-0.791). In all models, the predicted and observed risks in the high-risk groups were more than two times higher than the overall baseline risk. The classification of patients into low-, medium-, and high-risk groups in the second and third models agreed better with the actual occurrence of nursing home admission and death than that in the first model.

Conclusion

Using readily available routine healthcare data, we were able to adequately predict the risk of adverse health outcomes in community-dwelling older people. Our findings indicate that GPs can use the third, elaborate model as an automated frailty screening tool embedded in the EMR for proactive population-based care and can use the prediction rule with easily gathered predictors for case-finding during individual consultations.

Background

With increasing age, an individual's resilience gradually decreases. This process can result in a broad range of adverse health outcomes including multimorbidity, functional impairments, disabilities, and ultimately death.[1] A relatively high loss of resilience compared to others of the same age, with an increased risk of derailment after a relatively minor external stressor, is defined as frailty.[2]

Given their integrated approach and longitudinal relationships with their patients, general practitioners (GPs) play a coordinating role in the provision of care for older people.[3] To be able to guide this care to those who need it most, it is essential that GPs determine the level of frailty of older patients, both in population-based preventive programs and in individual consultations.[4]

Frailty can be identified with performance-based measurements, such as the Frailty Phenotype, or by questionnaires, such as the Tilburg Frailty Indicator.[5,6] These instruments may be difficult to implement in primary care settings because they require extra time and resources.[7] However, screening for frailty using routine care data registered in GPs' electronic medical records (EMRs) may help to overcome these limitations. This screening should be based on determinants predicting the occurrence of adverse health outcomes, such as nursing home admissions and mortality, which is, together with a Comprehensive Geriatric Assessment (GCA), currently considered the optimal reference standard for frailty.[8]

We recently evaluated the U-PRIM screening tool, an EMR-based instrument used for frailty screening. In the U-PRIM, the following factors are included: age; sex; polypharmacy, defined as five or more medications in chronic use; a consultation gap, defined as more than three years since the patient's last consultation; and the frailty index (FI).[9] Out of a predefined list, the FI score summarises the proportion of 'health deficits' present in a patient.[10] We demonstrated that screening for frailty in primary care with U-PRIM resulted in increased preservation of daily functioning in community-dwelling older people. Despite its demonstrated effectiveness, this type of frailty screening requires further improvement and fine-tuning. First, the U-PRIM screening instrument does not yet prioritise individual risk factors according to their relative contributions to the frailty risk or calculate such overall absolute risk. Second, the FI we incorporated in U-PRIM has a restricted score range compared to different FIs investigated in other studies, indicating that information loss occurred.[11] Third, we hypothesised that the assessment of frailty could be improved by incorporating major geriatric events, such as cognitive impairment or falling, as separate indicators.

Therefore, the aim of this study was to optimise risk assessment of frailty among older patients in primary care by evaluating comprehensive prognostic models developed from routine healthcare data, based on our previously developed U-PRIM frailty screening instrument.

Methods

Design, Setting, and Participants

We conducted a prognostic cohort study with a five-year follow-up period including 21 general practices that provide care to approximately 100,000 patients in the city of Utrecht, the Netherlands. All patients aged 60 years and older were eligible for inclusion.

Procedures and Measurements

Data from the participating 21 general practices were collected within the Julius General Practitioners Network (JGPN) database, which contains routine healthcare data extracted from EMRs using the software infrastructure of the Mondriaan Health Research Data Foundation.[12] To ensure pseudonymised data, personal data were encrypted through a trusted third party.[13] In these pseudonymised EMR data files, we used frailty screening software to identify potential frailty predictors for each patient at the baseline date of 1 January 2008. We then gathered outcome measurements for the five-year follow-up period continuing until 31 December 2012.

Outcome

Nursing home admission and mortality were considered the combined primary outcome. Of all the patients who had left the practice during the five-year follow-up period, the EMRs were screened for the presence of ICPC code A96 (death) and for key words related to death or nursing home admission in the twelve months prior to the date of leaving the practice population (query syntax available upon request). Only a given patient's first registered adverse event was considered an outcome, with the departure date from the general practice as a proxy for the date of outcome occurrence. Follow-up time was calculated from the baseline date until the event date, the date of loss to follow-up, or until the end of the study. A research assistant checked whether the results of the automated screening procedure matched with the consultation notes in the pseudonymised EMR data.

Predictors

As potential predictors of adverse outcomes, we gathered the following data:

Patient demographics

We extracted information on the patients' sex and age.

Polypharmacy

Polypharmacy was defined as five or more medications in chronic use registered with Anatomic Therapeutic Chemical (ATC) codes.[14-16] Chronic use was defined in three ways: the prescription was set on 'chronic use'; the prescription came with at least two repeat prescription allowances; or at least three single prescriptions were encountered successively, including at least one prescription in the preceding 6 months.

Consultation gap

To detect possible care-avoiders, we considered the number of months between patients' last contact with the practice and the baseline date of 1 January 2008 as the consultation gap.[17] Influenza vaccination, ordering repeat prescriptions, and actions not directly involving patient contact were not counted as GP contacts.

Frailty index

Previously, we constructed an FI solely based on ICPC-encoded routine care data. The scores of this FI range from 0 to 0.42, with a considerably lower upper limit than in other FI studies worldwide.[11] Therefore, in the current study, we upgraded this FI by adding more symptoms and using not only ICPC-coded, but also ATC-coded, and diagnostic measurement data based on the available literature on FI and the disease burden in older people.[8,18,19] The approach we took to construct an FI has been described elsewhere.[11] In brief, we arranged the selected items into clinically relevant single- and multi-item deficits with an expected prevalence of at least 1%.[20] This resulted in an FI with 50 deficits (see appendix 1). We screened all patients for the presence of deficits at baseline, and the FI score was defined as the proportion of deficits present in a patient out of the predefined list of 50 deficits. For example, 20 deficits would result in an FI score of 0.40. The FI score theoretically ranges from zero (completely fit) to one (extremely frail), can be used to predict adverse health outcomes, and was shown to correlate well with other frailty measures such as the aforementioned Frailty Phenotype.[21,22]

Geriatric events, psychosocial events, and multimorbidity

We considered immobility/instability, cognitive impairment, and incontinence symptoms, which had been registered in the EMR during the three months prior to baseline either as new or on-going episodes, as geriatric events.[23-25] Furthermore, we defined mood disorders and social problems registered in the EMR during the previous three months as psychosocial events.[26,27] Finally, the following chronic diseases and impairments were considered as potential predictors of frailty when registered in the EMR in the past five years: cancer, ischemic heart disease, heart failure, TIA/CVA, arthritis/osteoarthrosis, COPD/asthma, diabetes mellitus, visual impairment, and hearing impairment.[28,29] The abovementioned geriatric events, psychosocial events, chronic diseases and impairments were also incorporated in the FI, but as equally weighted deficits. To explore their individual predictive value, we also considered these events as separate predictors, either instead or in addition to the FI score. Geriatric events, psychosocial events, chronic diseases and impairments were identified using a combination of International Classification of Primary Care (ICPC) codes, Anatomic Therapeutic Chemical (ATC) codes, and diagnostic test results from the EMRs of the participating practices (see appendix 2).[30]

Statistical analyses

First, we described the baseline characteristics of the total study sample and of patients with and without an adverse health outcome. Univariable and multivariable associations of the predictors with nursing home admission or death during follow-up were studied with Cox regression analysis. The linearity assumption for the association between continuous predictors and the outcome was assessed with restrictive cubic splines.[31] The discriminative ability of the models was studied with Harrell's c-statistic, which is equivalent to the area under the ROC curve for dichotomous outcomes.[31]

Model development

We constructed three models to predict adverse health outcomes. The first model closely reflected the original U-PRIM screening instrument and included age, sex, polypharmacy, consultation gap, and the FI. The second model included age, sex, polypharmacy, consultation gap, geriatric events, psychosocial events, and multimorbidity, which was defined as the presence of two or more of the chronic diseases and impairments that were assessed at baseline.[32] The last three of these factors, i.e., the presence of any geriatric event, the presence of any psychosocial event, and the presence of multimorbidity in the preceding three months, were used as

combined dichotomous predictors. In the second model, the FI was not included as a predictor. In the third model, we used all predictors that were considered relevant based on the available literature and clinical expertise and were available in the EMR, including age, sex, polypharmacy, consultation gap, FI, geriatric events, psychosocial events, and chronic diseases and impairments. In contrast to model 2, we included all individual events, diseases and impairments as separate predictors in model 3; for example, instead of the grouped predictor 'presence of any geriatric event' in model 2, we used the three separate predictors 'presence of instability/immobility', 'presence of cognitive impairment', and 'presence of incontinence' in the third model. We internally validated all models with bootstrapping strategies. Furthermore, we derived a shrinkage factor and evaluated the optimism in the c-statistic.[31,33]

For all three models, we evaluated the observed and predicted risks for low-, medium-, and high-risk groups at one and five years. The cut-off values for the risk groups were chosen such that each risk group contained one-third of the study population. For the second and third models, we constructed survival curves. In addition, we constructed reclassification tables for one- and five-year risk of adverse health outcomes comparing the second and third models to the first basic model, and we also calculated the net reclassification improvements (NRIs).[34] We performed these analyses using SPSS (Version 20.0, Armonk, NY, IBM Corp.) and the rms package in R (Version 2.15.0). For statistical tests, the significance level was set at a p-value of < 0.05.

Ethics

Because this study used pseudonymised patient EMR data, assessment by the local institutional review board was not required.

Results

Three general practices were excluded due to technical problems with data extraction from the EMR. For the remaining 18 general practices, we included all 13420 patients aged 60 years or older at baseline (Table 1). Of these, 7443 (55.5%) patients were female, and the mean age was 71.01 years (SD 8.58). Seven patients had a consultation gap ranging from 66 to 108 years. We assumed that this was due to administrative errors, and replaced this figure by the mean consultation gap of the 13413 other patients. During the observation period, 1765 patients (13.2%) were lost to follow-up, due to either moving to another independent living situation outside of the area (n = 721, 5.4%), moving to an assisted living facility (n = 175, 1.3%), or for unknown reasons (n = 869, 6.5%).

Table 1. Baseline characteristics

Variable	All patients N = 13420	Patients with adverse outcomes during follow-up N = 2013	Patients without adverse outcomes during follow-up N = 11407
Age, mean (SD)	71.01 (8.58)	78.14 (9.15)	69.75 (7.83)
Female, n (%)	7443 (55.5)	1097 (54.5)	6346 (55.6)
Polypharmacy, n (%)	3251 (24.2)	831 (41.3)	2420 (21.2)
FI score, median (IQR)	0.12 (0.06 - 0.20)	0.18 (0.10 – 0.26)	0.12 (0.06-0.18)
Consultation gap in months, median (IQR)	1 (0 – 3)	1 (0-2)	2 (1-3)
Geriatric events			
Instability / immobility, n (%)	1941 (14.5)	402 (20)	1539 (13.5)
Cognitive impairment, n (%)	335 (2.5)	161 (8.0)	174 (1.5)
Urinary incontinence, n (%)	545 (4.1)	188 (9.3)	357 (3.1)
≥ 1 Geriatric event, n (%)	2522 (18.8)	617 (30.7)	1905 (16.7)
Psychosocial events			
Mood disorders, n (%)	1762 (13.1)	401 (19.9)	1361 (11.9)
Social problems, n (%)	189 (1.4)	44 (2.2)	145 (1.3)
≥ 1 Psychosocial event, n (%)	1880 (14.0)	433 (21.5)	1447 (12.7)
Chronic diseases and impairments			
Cancer, n (%)	1559 (11.6)	420 (20.9)	1139 (10.0)
Ischemic heart disease, n (%)	2261 (16.8)	515 (25.6)	1746 (15.3)
Heart failure, n (%)	750 (5.6)	325 (16.1)	425 (3.7)
TIA / CVA, n (%)	882 (6.6)	261 (13.0)	621 (5.4)
Arthritis / osteoarthrosis, n (%)	2853 (21.3)	496 (24.6)	2357 (20.7)
COPD / asthma, n (%)	2872 (21.4)	584 (29.0)	2288 (20.1)
Diabetes mellitus, n (%)	2740 (20.4)	518 (25.7)	2222 (19.5)
Visual impairment, n (%)	1497 (11.2)	333 (16.5)	1164 (10.2)
Hearing impairment, n (%)	677 (5.0)	145 (7.2)	532 (4.7)
Multimorbidity yes/noa, n (%)	4525 (33.7)	1054 (52.4)	3471 (30.4)

In total, 2013 patients (15%) experienced an adverse health outcome; of these, 375 patients (2.8%) were admitted to a nursing home, and 1638 patients (12.2%) died. Patients with an adverse health outcome were older and had a worse overall health status at baseline compared to patients without an adverse health outcome.

The median FI score was 0.12 (IQR 0.06 – 0.20) with a right-skewed distribution (Figure 1). The deficit prevalence ranged from 2.4% for the deficits 'treatment complications' and 'liver/gall bladder disease' to 50.4% for the 'hypertension' deficit (see appendix 1).

Univariable Cox regression analyses demonstrated that with the exception of sex, all predictors were significantly associated with an increased risk of adverse health outcomes (Table 2). The continuous predictors of age (HR 1.111, 95% CI 1.106 – 1.117) and FI score (HR 1.110, 95% CI 1.102 – 1.119) and the dichotomous predictor of cognitive impairment (HR 5.117, 95% CI 4.354 – 6.013) showed the strongest associations. As the consultation gap did not demonstrate a linear relationship with adverse health outcomes, it was transformed into a categorical variable including the following three groups: 0 months, 1-12 months, and ≥ 12 months.

Figure 1. Frailty Index distribution

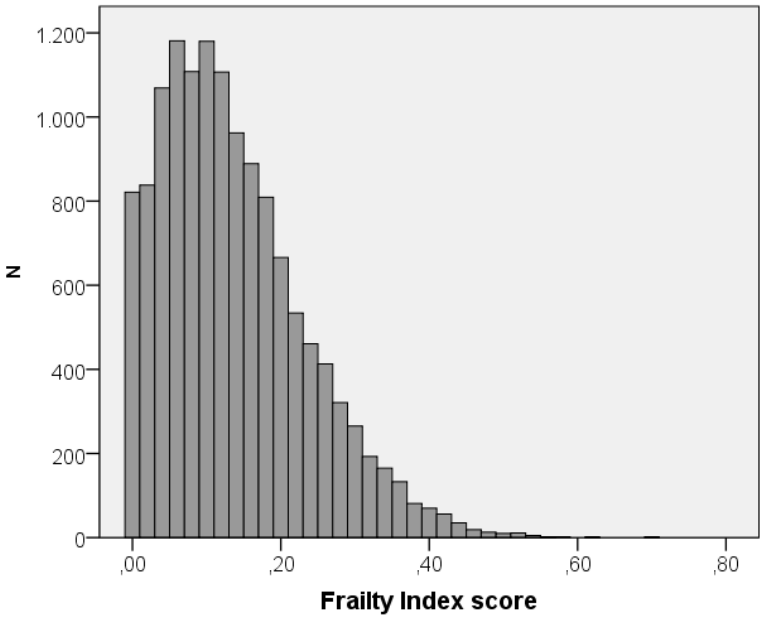


Table 2. Univariable relationship of frailty-related factors with adverse health outcomes

	Beta	P-value	Hazard Ratio (95% CI)
Age	0.105	< 0.001	1.111 (1.106 – 1.117)
Sex	-0.034	0.451	0.967 (0.886 – 1.055)
Polypharmacy	0.900	< 0.001	2.460 (2.251 – 2.689)
Consultation gap:			
Consultation gap 1-12 months	-0.604	< 0.001	0.547 (0.500 – 0.598)
Consultation gap > 12 months	-1.030	< 0.001	0.357 (0.285 – 0.448)
FI score	0.105	< 0.001	1.110 (1.102 – 1.119)
Geriatric Events:			
Instability / immobility	0.458	< 0.001	1.581 (1.417 – 1.764)
Cognitive impairment	1.633	< 0.001	5.117 (4.354 – 6.013)
Urinary incontinence	1.110	< 0.001	3.036 (2.612 – 3.528)
≥ 1 Geriatric event	0.764	< 0.001	2.147 (1.953 – 2.361)
Psychosocial Events:			
Mood disorders	0.577	< 0.001	1.781 (1.596 – 1.987)
Social problems	0.512	< 0.001	1.668 (1.238 – 2.249)
≥ 1 Psychosocial event	0.602	< 0.001	1.825 (1.641 – 2.030)
Chronic diseases and impairments:			
Cancer	0.798	< 0.001	2.221 (1.995 – 2.474)
Ischemic heart disease	0.601	< 0.001	1.823 (1.650 – 2.015)
Heart failure	1.452	< 0.001	4.272 (3.793 – 4.812)
TIA / CVA	0.888	< 0.001	2.430 (2.134 – 2.768)
Arthritis / osteoarthrosis	0.223	< 0.001	1.250 (1.129 – 1.383)
COPD / asthma	0.447	< 0.001	1.563 (1.419 – 1.721)
Diabetes mellitus	0.340	< 0.001	1.405 (1.272 – 1.553)
Visual impairment	0.524	< 0.001	1.689 (1.501 – 1.899)
Hearing impairment	0.415	< 0.001	1.515 (1.279 – 1.793)
Multimorbidity	0.873	< 0.001	2.393 (2.193 – 2.612)

Effects are presented per one-year increase in age and per deficit increase in the FI. Male sex, a consultation gap of zero months, and the absence of the other respective categorical variables were used as reference values. CI = confidence interval, FI = Frailty Index.

Notably, whereas sex was not a significant predictor in the univariable Cox regression analyses, male sex was significantly associated with the risk of adverse health outcomes in all multivariable models (Table 3). Furthermore, a consultation gap of less than one month and a consultation gap of more than 12 months were both associated with an increased risk of adverse health outcomes compared to a consultation gap of 1 to 12 months in each model. In the third model, instability/immobility, social problems, ischemic heart disease, diabetes mellitus and visual impairment were not significantly associated with adverse health outcomes.

Both the first and second model demonstrated good discriminative ability (Table 3: c-statistic 0.765 (95% CI 0.755 – 0.775) for model 1 and 0.0766 (95% CI 0.756 – 0.777) for model 2). The third model revealed slightly better discriminative ability than the first two models (c-statistic 0.781 (95% CI 0.77 – 0.791)). After bootstrapping, the internal shrinkage factors for all models varied from 0.989 to 0.998. This indicated good internal validity and minimal optimism, so the beta coefficients were left unadjusted. For each model, the predicted risks in the high-risk groups were more than two times higher than the baseline risks in the overall population (Table 4). Because model 2 consisted of a limited set of predictors, which were all readily available during consultation of individual patients, the second model was transformed into a clinical prediction rule (Table 5). The prediction rule showed comparable results to the model it was derived from. Survival curves of the risk groups of all three models demonstrated that high-risk groups had a significantly higher risk of adverse health outcomes than the medium- and low-risk groups (Figure 2 for survival curves model 3). When compared to the first model, the NRI for the one-year risk of adverse health outcomes was 0.9% for the second model and 6.5% for the third model (Appendix 3). For the five-year risk of adverse health outcomes, the NRI was 0.3% for the second model and 3.6% for the third model.

Table 3. Multivariable models and their relationship with adverse health outcomes

	Beta	P-value	Hazard Ratio (95% CI)	C-statistic (95% CI)
MODEL 1				**0.765 (0.755-0.775)**
Age	0.100	< 0.001	1.105 (1.099 – 1.111)	
Sex	- 0.397	< 0.001	0.672 (0.615 – 0.736)	
Polypharmacy	0.193	0.001	1.213 (1.084 – 1.359)	
Consultation gap 1-12 months	- 0.178	< 0.001	0.837 (0.759 – 0.923)	
Consultation gap > 12 months	0.059	0.634	1.061 (0.832 – 1.353)	
FI	0.048	< 0.001	1.050 (1.038 – 1.061)	
MODEL 2				**0.766 (0.756-0.777)**
Age	0.100	< 0.001	1.105 (1.099 – 1.111)	
Sex	- 0.398	< 0.001	0.671 (0.613 – 0.735)	
Polypharmacy	0.318	< 0.001	1.374 (1.244 – 1.519)	
Consultation gap 1-12 months	- 0.216	< 0.001	0.805 (0.732 – 0.886)	
Consultation gap > 12 months	- 0.052	0.671	0.950 (0.749 – 1.204)	
Geriatric events	0.241	< 0.001	1.273 (1.151 – 1.408)	
Psychosocial events	0.295	< 0.001	1.343 (1.201 – 1.503)	
Multimorbidity	0.227	< 0.001	1.256 (1.139 – 1.384)	
MODEL 3				**0.781 (0.771-0.791)**
Age	0.097	< 0.001	1.102 (1.096 – 1.108)	
Sex	- 0.313	< 0.001	0.731 (0.666 – 0.802)	
Polypharmacy	0.163	0.006	1.177 (1.049 – 1.322)	
Consultation gap 1-12 months	- 0.173	0.001	0.841 (0.761 – 0.930)	
Consultation gap > 12 months	0.072	0.564	1.075 (0.841 – 1.374)	
FI	0.021	0.006	1.021 (1.006 – 1.037)	
Instability / immobility	0.007	0.913	1.007 (0.896 – 1.131)	

	Beta	P-value	Hazard Ratio (95% CI)	C-statistic (95% CI)
Cognitive impairment	0.951	< 0.001	2.589 (2.186 – 3.067)	
Urinary incontinence	0.232	0.004	1.261 (1.077 – 1.476)	
Mood disorders	0.161	0.011	1.175 (1.038 – 1.329)	
Social problems	0.025	0.872	1.025 (0.758 – 1.386)	
Cancer	0.414	< 0.001	1.513 (1.353 – 1.691)	
Ischemic heart disease	- 0.061	0.280	0.941 (0.843 – 1.051)	
Heart failure	0.590	< 0.001	1.804 (1.584 – 2.055)	
TIA / CVA	0.279	< 0.001	1.322 (1.154 – 1.514)	
Arthritis / osteoarthrosis	- 0.244	< 0.001	0.784 (0.702 – 0.875)	
COPD / asthma	0.204	< 0.001	1.227 (1.105 – 1.362)	
Diabetes mellitus	0.094	0.088	1.098 (0.986 – 1.223)	
Visual impairment	- 0.098	0.118	0.907 (0.803 – 1.025)	
Hearing impairment	- 0.216	0.015	0.806 (0.677 – 0.958)	

Effects are presented per one-year increase in age and per deficit increase in the FI. Male sex, a consultation gap of zero months, and the absence of the other respective categorical variables were used as reference values. CI = confidence interval. FI = Frailty Index.

Table 4. Comparison of predicted and observed risks at one and five years for all multivariable models

Model	One-year predicted risks	One-year observed risks	Five-year predicted risks	Five-year observed risks
Model 1				
Low risk	0.8%	0.8% (34/4472)	4.4%	4.3% (193/4472)
Medium risk	1.8%	1.7% (75/4475)	10.5%	9.4% (422/4475)
High risk	7.7%	7.7% (343/4473)	35.3%	31.3% (1398/4473)
Total	3.4%	3.4% (452/13420)	16.7%	15.0% (2013/13420)
Model 2				
Low risk	0.8%	0.7% (32/4474)	4.5%	4.2% (189/4474)
Medium risk	1.9%	1.7% (75/4464)	10.6%	9.5% (423/4464)
High risk	7.6%	7.7% (345/4482)	35.0%	31.3% (1401/4482)
Total	3.4%	3.4% (452/13420)	16.7%	15.0% (2013/13420)
Model 3				
Low risk	0.7%	0.6% (26/4473)	4.4%	4.0% (179/4473)
Medium risk	1.7%	1.4% (63/4474)	10.1%	8.7% (389/4474)
High risk	8.0%	8.1% (363/4473)	35.6%	32.3% (1445/4473)
Total	3.5%	3.4% (452/13420)	16.7%	15.0% (2013/13420)

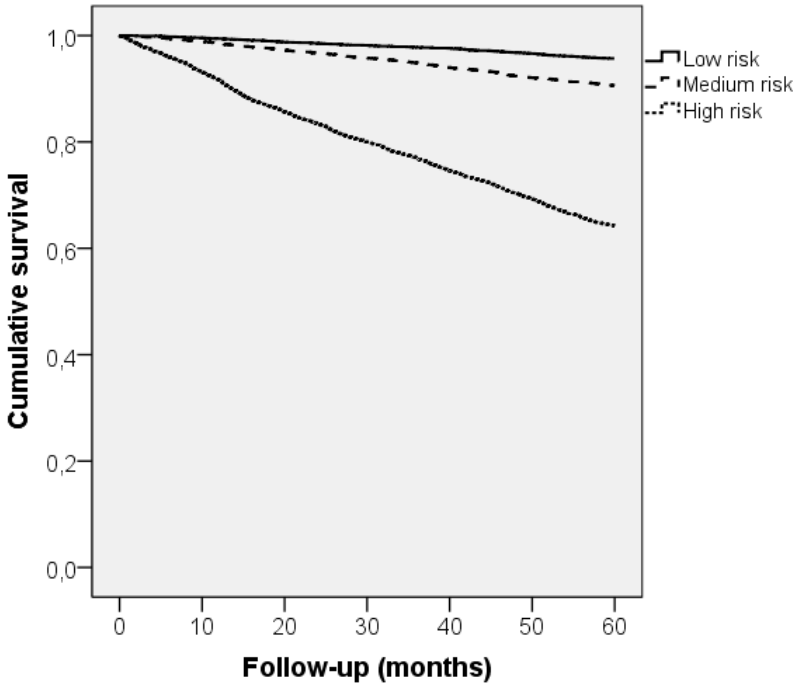
Table 5. Score chart of the prediction rule based on model 2 to calculate the predicted risk of adverse health outcomes at one and five years

	Points				
Predictor	**0**	**1**	**2**	**3**	**4**
Age	The number of points is the patient's age minus 60				
Sex	Female				Male
Polypharmacy	No			Yes	
Consultation gap	1-12 months	More than 12 months	Less than 1 month		
Any geriatric event	No		Yes		
Any psychosocial event	No			Yes	
Multimorbidity	No		Yes		

Risk group	**One-year predicted risks**	**One-year observed risks**	**Five-year predicted risks**	**Five-year observed risks**
Low risk (< 14 points)	0.7%	0.7% (31/4275)	4.3%	4.2% (180/4275)
Medium risk (14 – 23 points)	1.8%	1.6% (76/4628)	10.3%	9.2% (427/4628)
High risk (> 23 points)	7.7%	7.6% (345/4517)	35.1%	31.1% (1406/4517)
Overall risk	3.4%	3.4% (452/13420)	16.7%	15.0% (2013/13420)

The prediction rule is based on 'Model 2' as presented in Table 3. Beta values were multiplied by ten and rounded to give the number of points per predictor. The upper panel shows the points corresponding to each predictor value. The points are summed into a total score. Based on their score, patients were classified into one of the following risk groups: low risk (< 14 points), medium risk (14 – 23 points), and high risk (> 23 points). The cut-off values for the risk groups were chosen such that the study population was divided into three equal groups. The corresponding risks for adverse health outcomes at one and five years can be found in the lower panel in the columns entitled 'predicted risks'. For comparison, the observed percentage of patients with adverse health outcomes is shown in the columns entitled 'observed risks'. The following serves as an example to illustrate the use of the score chart. A 75-year old man with 8 medications in chronic use, 3 weeks of time elapsed since his last consultation, with a recent fall, and with diabetes, heart failure, and arthritis received a score of 15 (age) + 4 (sex) + 3 (polypharmacy) + 2 (consultation gap < 1 month) + 2 (any geriatric event) + 2 (multimorbidity) = 28 points. According to the prediction rule, this patient is in the high-risk group, resulting in a mean predicted one and five year risk of adverse health outcomes of 7.7% and 35.1%, respectively.

Figure 2. Survival curves for low-, medium-, and high-risk groups based on model 3



Discussion

Summary of results

We demonstrated that prognostic models based on different sets of clinical information extracted from routine primary care data could adequately predict adverse health outcomes in older patients. Moreover, the models applied showed good discriminative ability. Patients classified in high-risk groups had greater than a two-fold higher risk of adverse health outcomes, both for one- and five-year risk, than the overall baseline risk. The outcome of risk assessment with a dataset including age, sex, consultation gap, polypharmacy and the FI (model 1, representing the original UPRIM instrument) was comparable to assessment with the FI replaced with information about recent geriatric events, psychosocial events and longstanding multimorbidity (model 2). The NRI for one- and five-year risk of adverse health outcomes was 0.8% and 0.3%, respectively, for the second model compared to the first model. The third, most extended model, which included all relevant available EMR information, demonstrated slightly better predictive performance compared to the first two models. The NRI of the third model compared to the first model was 6.5% and 3.6% for one- and five-year risk of adverse health outcomes, respectively.

The increase in discriminatory ability of the third, extended model compared to the other models may be perceived as small. However, we believe this is a clinically relevant difference, as a relatively minor increase in discriminatory ability, with a resulting improvement in care, may produce greater health benefits at the population level. This is further supported by the NRIs. Moreover, this approach would enable optimal targeting of personalised proactive care to those with the greatest needs.

At a value of 0.70, the upper limit of the revised FI used as a predictor in this study was equal to that found in other FI studies worldwide. This limit is considered the maximum proportion of accumulated deficits, beyond which survival does not seem possible.[20] We used an unweighted FI to define a generalisable measure of overall health status. In the extended prognostic model, we demonstrated that adding high-impact individual health deficits as separate predictors to the FI could improve the predictive performance of the overall model; the presence of cognitive impairment with a HR of 2.589 (95% CI 2.186 – 3.067) was the best example. However, some of the individual predictors, such as instability/immobility, social problems, diabetes, ischemic heart disease and visual impairment, did not make significant contributions to the model, which may indicate that their predictive ability was already covered sufficiently by the FI.

In all multivariable models, a moderate consultation gap was associated with the lowest risk of adverse health outcomes. The high risk observed in patients with a short

consultation gap likely reflects a higher burden of disease, whereas the high risk associated with a prolonged consultation gap may indicate the increased risk of adverse health outcomes among care avoiders.

Whereas sex was not predictive for adverse health outcomes in the univariable model, men were at an increased risk of such outcomes in all multivariable models. Given patients with similar health states and ages, this indicates that men have a higher risk of mortality and nursing home admission than women, which has been commonly reported in other studies.[35] Moreover, the finding that this association only appeared in the multivariable models is likely due to confounding by age, which masked the association in the crude analysis. Indeed, the mean age of women was significantly higher than the mean age of men (72.15 years vs. 69.93 years, p-value < 0.001).

Strengths and limitations

This study had certain limitations. First, there was a risk of informative censoring, i.e., that the reasons for loss to follow-up were related to the assessment of the outcome.[36] On average, patients lost to follow-up were older and in worse health states, and therefore potentially at higher risk of adverse health outcomes, compared to patients who completed follow-up. This could have led to conservative parameter estimates in our model. Second, we only included nursing home admission and mortality and did not include other adverse outcomes such as emergency department visits or hospital admissions. These outcomes could not reliably be extracted in an automated process. Third, the quality and reliability of routine care data in EMRs may differ, especially in the registration of social problems, functional impairments, and cognitive impairment. However, different international studies have shown that data registration by GPs in the EMR is generally adequate and sufficient to explore a more elaborate use of routine care data.[37,38]

Our study also had a number of strengths. First, we included a large sample of older patients from a diverse range of general practices, thereby enhancing generalisability of our results. Second, all models were based on routinely available EMR data, which promotes simple implementation in daily clinical care and makes our results of high practical relevance. Third, as recommended, we used a modelling approach with predictor selection based on predefined clinical reasoning and relevance, instead of relying on data-driven approaches such as backward selection, which may lead to unstable models with a reduced performance in new patients.[31,39] Internal validation resulted in shrinkage factors very close to one, demonstrating almost no optimism. Fourth, to find a balance between optimal data collection and maximum flexibility in

follow-up FI scores, we attempted to adjust the observation periods to the deficit nature – changeable or not changeable – considering potential on-going impact of the deficit on the patients' health state after EMR episode closure and registration variability. However, whereas this strategy enabled the FI to be a dynamic score that could improve over time, this approach requires further exploration and refinement. Fifth, we used a relatively low inclusion criterion of 60 years and older due to the high number of first-generation non-Western immigrants, who may become frail at a relatively young age.[40]

Comparison with other research

In the literature, studies on the development and evaluation of frailty screening instruments, specifically for use in primary care, are scarce.[3] In a recent systematic review of frailty screening tools suitable for primary care, ten different instruments were identified, and only two were tested in studies recruiting patients directly from GP consultations: the Tilburg Frailty Indicator (TFI) and the SHARE instrument.[41] The TFI is a self-administered questionnaire assessing 15 items in the physical, psychological and social domains, and this indicator is predictive of quality of life, autonomy and many indicators of healthcare use.[42] In particular, areas under the curve varied from 0.54 (95% CI 0.43-0.66) for the prediction of GP consultations to 0.83 (95% CI 0.77-0.88) for the prediction of disability. This indicator also requires an average of 14 minutes for administration, making it more suitable as a follow-up screening step than a primary screening method. The SHARE instrument is an online calculator that determines a patient's frailty class based on five measurements; this method demonstrated a discriminatory ability for 5-year mortality risk of 0.70 (95% CI 0.68-0.72).[43,44] Although this instrument has good construct and criterion validity, GPs would need to use performance-based measures that may take considerable time to complete, so it's applicability in daily clinical practice has yet to be determined. A third example is the Gérontopôle Frailty Screening Tool (GFST), consisting of a questionnaire and clinical judgement by the GP, after which optional referral to a frailty clinic is performed.[45] Whereas 95.2% of the referred patients presented with a (pre-)frail condition according to the phenotypic frailty criteria, this instrument was designed to be used in patients without physical disability and acute clinical disease, thus limiting its use in daily clinical practice.

Implications for clinical practice

The models we developed can be used to improve primary care for older people in two main ways. The first approach consists of using model 3 as the first step in population or

panel management.[46] In panel management, the practice population would be systematically screened for frailty using a software application embedded in the EMR system based on the elaborate prognostic model. This software application generates a report of older patients at risk of frailty, and then GPs and practice nurses can act upon this report by providing proactive care, such as polypharmacy reviews, performing a comprehensive geriatric assessment, and implementing individual care plans. Panel management of older patients, consisting of quarterly frailty screenings followed by a comprehensive geriatric assessment and individual care plans by practice nurses, has also been shown to be a cost-effective strategy for care in frail older people (chapter 7). This strategy enables GPs to improve risk assessment of all older people in their practice without the need to see each patient individually. The third model is an extension of the first model reflecting the U-PRIM frailty selection instrument, which was originally developed and evaluated in the U-PROFIT trial. The slightly better predictive performance of this elaborate third model demonstrates that the selection processes in panel management can be further improved.

In the second approach, the prediction rule, derived from the second model, can be used during consultation to estimate the risk of adverse health events of individual patients, thereby tailoring decisions on diagnostic or therapeutic management to individual risk profiles.[47] As such, this prediction rule could be used for case finding of frail older patients during individual patient consultations for surgery.

In conclusion, prognostic models based on EMR information can adequately assess patients' risk of adverse health outcomes and support primary care health professionals in providing proactive, tailored care to older patients at risk of frailty. This may result in a more efficient allocation of interventions and improvements in patient health status, level of daily functioning, and quality of life. However, both the third (elaborate) prognostic model and the prediction rule we derived from the second model need to be evaluated further. In particular, the predictive ability for other outcome measures should be explored, the correlation of predicted risks with a CGA or with other frailty measures should be addressed, and external validation is required.

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Appendix 1. Frailty Index deficits

Deficit	Deficit name	Deficit prev.	Code[a]	Description	Days[c]
1	General signs and symptoms	15.0	A01[a]	Pain general/multiple sites	183
			A03[a]	Fever	183
			A04[a]	Weakness/tiredness general	183
			A05[a]	General deterioration	183
			A29[a]	General symptom/complaint other	183
			B29[a]	Sympt/Complt lymph/immune other	183
			N02[b]	Analgesics	183
2	Instability/ immobility	31.0	A06[a]	Fainting/syncope	183
			A10[a]	Bleeding-haemorrhage NOS	183
			A28[a]	Limited function/disability NOS	1825
			A80[a]	Trauma/injury NOS	183
			H82[a]	Vertiginous syndrome / labyrinthitis	1825
			K88[a]	Postural hypotension	1825
			L02[a]	Back symptom/complaint	183
			L03[a]	Low back symptom/complaint without radiating pain	183
			L13[a]	Hip symptom/complaint	183
			L14[a]	Leg/thigh symptom/complaint	183
			L15[a]	Knee symptom/complaint	183
			L16[a]	Ankle symptom/complaint	183
			L17[a]	Foot/toe symptom/complaint	183
			L28[a]	Limited function/disability	1825
			L72[a]	Fracture: radius/ulna	1825
			L73[a]	Fracture: tibia/fibula	1825
			L74[a]	Fracture: hand/foot bone	1825
			L75[a]	Fracture: femur	1825
			L76[a]	Fracture: other	1825
			L77[a]	Sprain/strain of ankle	183
			L78[a]	Sprain/strain of knee	183
			L79[a]	Sprain/strain of joint NOS	183
			L80[a]	Dislocation/subluxation	1825
			L81[a]	Injury musculoskeletal NOS	183
			L86[a]	Low back symptom/complaint with radiating pain	183
			L96[a]	Acute internal damage knee	1825

Deficit	Deficit name	Deficit prev.	Code[a]	Description	Days[c]
			N17[a]	Vertigo/dizziness	183
			N18[a]	Paralysis/weakness	1825
			N79[a]	Concussion	1825
			N80[a]	Head injury other	1825
			S16[a]	Bruise/contusion	183
			S17[a]	Abrasion/scratch/blister	183
			S18[a]	Laceration/cut	183
			S19[a]	Skin injury other	183
			N07C[b]	Antivertigo drugs	1825
			Med	decubitus	1825
			Med	Wound[a] OR stitch[a] OR sling	183
3	Treatment complications	2.4	A13[a]	Concern/fear medical treatment	183
			A85[a]	Adverse effect medical agent	183
			A87[a]	Complication of medical treatment	183
			A89[a]	Effect prosthetic device	183
4	Cancer	11.6	A79[a]	Malignancy NOS	1825
			B72[a]	Hodgkin's disease	1825
			B73[a]	Leukaemia	1825
			B74[a]	Malignant neoplasm blood other	1825
			D74[a]	Malignant neoplasm stomach	1825
			D75[a]	Malignant neoplasm colon/rectum	1825
			D76[a]	Malignant neoplasm pancreas	1825
			D77[a]	Malig. neoplasm digest other/NOS	1825
			F74[a]	Neoplasm of eye/adnexa	1825
			H75[a]	Neoplasm of ear	1825
			K72[a]	Neoplasm cardiovascular	1825
			L71[a]	Malignant neoplasm musculoskeletal	1825
			N74[a]	Malignant neoplasm nervous system	1825
			R84[a]	Malignant neoplasm bronchus/lung	1825
			S77[a]	Malignant neoplasm of skin	1825
			T71[a]	Malignant neoplasm thyroid	1825
			U75[a]	Malignant neoplasm of kidney	1825
			U76[a]	Malignant neoplasm of bladder	1825
			U77[a]	Malignant neoplasm urinary other	1825
			X75[a]	Malignant neoplasm cervix	1825
			X76[a]	Malignant neoplasm breast female	1825

Deficit	Deficit name	Deficit prev.	Code[a]	Description	Days[c]
			X77[a]	Malignant neoplasm genital other (f)	1825
			Y77[a]	Malignant neoplasm prostate	1825
			Y78[a]	Malignant neoplasm male genital / mammae	1825
			L01[b]	Antineoplastic agents	1825
			L02[b]	hormonal agents given in malignant conditions	1825
5	Anemia	8.9	B80[a]	Iron deficiency anaemia	1825
			B81[a]	Anaemia, Vitamin B12/folate def.	1825
			B82[a]	Anaemia other/unspecified	1825
			B03[b]	Antianemic medications	1825
			Hb[d]	Haemoglobine measurement (< 8.0 mmol/L (male and < 70 yrs) OR < 6.9 mmol/L (male and ≥ 70 yrs) OR < 7.0 mmol/L (female and < 70) OR < 6.8 mmol/L (female and ≥ 70 yrs)	1825
6	GI tract symptoms	19.5	D01[a]	Abdominal pain/cramps general	183
			D02[a]	Abdominal pain epigastric	183
			D03[a]	Heartburn	183
			D06[a]	Abdominal pain localized other	183
			D09[a]	Nausea	183
			D10[a]	Vomiting	183
			D11[a]	Diarrhea	183
			D12[a]	Constipation	183
			D14[a]	Haematemesis/vomiting blood	183
			D15[a]	Melaena	183
			D16[a]	Rectal bleeding	183
			D17[a]	Incontinence of bowel	183
			D18[a]	Change faeces/bowel movements	183
			D20[a]	Mouth/tongue/lip symptom/complt.	183
			D29[a]	Digestive symptom/complaint other	183
			A04[b]	Antiemetics and antinauseants	183
			A07[b]	Antidiarrheals, intestinal anti-inflammatory/anti-infective agents	183
			A06[b]	Drugs for constipation	183
7	Liver/gallbladder disease	2.4	D72[a]	Viral hepatitis	1825
			D97[a]	Cirrhosis / liver disease NOS	1825

Deficit	Deficit name	Deficit prev.	Code[a]	Description	Days[c]
			D98[a]	Cholecystitis/cholelithiasis	1825
			A05[b]	Bile and liver therapy	1825
8	Upper GI tract disease / GI tract herniae	39.0	D73[a]	Gastroenteritis presumed infection	183
			D84[a]	Oesophagus disease	1825
			D85[a]	Duodenal ulcer	1825
			D86[a]	Peptic ulcer other	1825
			D87[a]	Stomach function disorder	1825
			D89[a]	Inguinal hernia	1825
			D90[a]	Hiatus hernia	1825
			A02[b]	Drugs for acid related disorders	1825
9	Lower GI tract disease	16.0	D92[a]	Diverticular disease	1825
			D93[a]	Irritable bowel syndrome	1825
			D94 [a]	Chronic enteritis/ulcerative colitis	1825
			K96[a]	Haemorrhoids	183
			A03[b]	Drugs for functional gastrointestinal disorders	1825
10	Eye symptoms / infections	8.9	F02[a]	Red eye	183
			F03[a]	Eye discharge	183
			F04[a]	Visual floaters/spots	183
			F05[a]	Visual disturbance other	183
			F13[a]	Eye sensation abnormal	183
			F15[a]	Eye appearance abnormal	183
			F16[a]	Eyelid symptom/complaint	183
			F70[a]	Conjunctivitis infectious	183
			F72[a]	Blepharitis/stye/chalazion	183
			F85[a]	Corneal ulcer	183
			S01A[b]	Anti-infectives	183
			S01X[b]	Other ophthalmologicals	183
			VIPB[d]	Visual complaints (if 1, then score positive, if 2, 8, or unknown then score negative)	183
11	Visual impairment	11.2	F83[a]	Retinopathy	1825
			F84[a]	Macular degeneration	1825
			F92[a]	Cataract	1825
			F93[a]	Glaucoma	1825
			F94[a]	Blindness	1825

Deficit	Deficit name	Deficit prev.	Code[a]	Description	Days[c]
			S01E[b]	Antiglaucoma preparations and miotics	1825
12	Ear symptoms / infection	7.2	H02[a]	Hearing complaints	183
			H03[a]	Tinnitus, ringing/buzzing ear	183
			H13[a]	Plugged feeling ear	183
			H70[a]	Otitis externa	183
			H81[a]	Excessive ear wax	183
			S02[b]	Otologicals	183
13	Hearing impairment	5.0	H84[a]	Presbyacusis	1825
			H86[a]	Deafness	1825
14	Circulatory tract symptoms	5.5	K01[a]	Heart pain	183
			K02[a]	Pressure/tightness of heart	183
			K04[a]	Palpitations / awareness of heart	183
			K07[a]	Swollen ankles/oedema	183
			K29[a]	Cardiovascular sympt./complt. other	183
			ANGK[d]	Symptoms of Angina Pectoris (if 1, then score positive, if 2, 8, or unknown then score negative)	183
			DETK[d]	Symptoms of heart failure (if 1, then score positive, if 2, 8, or unknown then score negative)	183
15	Ischemic heart disease	16.8	K74[a]	Angina pectoris	1825
			K75[a]	Acute myocardial infarction	1825
			K76[a]	Other / chronic ischaemic heart disease	1825
			C01DA[b]	Organic nitrates	1825
16	Heart failure	5.6	K77[a]	Heart failure	1825
17	Cardiac arrhythmias / heart valve disease	10.6	K78[a]	Atrial fibrillation/flutter	1825
			K79[a]	Paroxysmal tachycardia	1825
			K80[a]	Cardiac arrhythmia NOS	1825
			K83[a]	Heart valve disease NOS	1825
			C01A[b]	Cardiac Glycosides	1825
			C01B[b]	Antiarrythmics class I and III	1825
18	Hypertension	50.4	K85[a]	Elevated blood pressure	1825
			K86[a]	Hypertension uncomplicated	1825
			K87[a]	Hypertension complicated	1825
			C02[b]	Antihypertensives	1825

Deficit	Deficit name	Deficit prev.	Code[a]	Description	Days[c]
			RRSY[d]	Systolic blood pressure ≥ 140 mm/Hg	1825
			RRDI[d]	Diastolic blood pressure ≥ 90 mm/Hg	1825
19	TIA/CVA	6.6	K89[a]	Transient cerebral ischaemia	1825
			K90[a]	Stroke/cerebrovascular accident	1825
20	Peripheral vascular disease / thrombotic disease	10.6	K91[a]	Atherosclerosis	1825
			K92[a]	other PVD	1825
			K93[a]	Pulmonary embolism	1825
			K94[a]	Phlebitis/thrombophlebitis	1825
			K99[a]	Cardiovascular disease other	1825
			Med	Stocking OR bandage st	1825
21	Locomotor tract symptoms	11.3	L01[a]	Neck symptom/complaint	183
			L04[a]	Chest symptom/complaint	183
			L05[a]	Flank/axilla symptom/complaint	183
			L08[a]	Shoulder symptom/complaint	183
			L09[a]	Arm symptom/complaint	183
			L10[a]	Elbow symptom/complaint	183
			L11[a]	Wrist symptom/complaint	183
			L12[a]	Hand/finger symptom/complaint	183
			L18[a]	Muscle pain	183
			L19[a]	Muscle symptom/complaint NOS	183
			L20[a]	Joint symptom/complaint NOS	183
			L29[a]	Sympt/complt. Musculoskeletal other	183
			L92[a]	Shoulder syndrome	183
22	Arthritis / Osteoarthrosis	21.3	L84[a]	Arthrosis/spondylosis back	1825
			L88[a]	Rheumatoid arthritis / related condition	1825
			L89[a]	Osteoarthrosis of hip	1825
			L90[a]	Osteoarthrosis of knee	1825
			L91[a]	Osteoarthrosis other / related condition	1825
			M01AH[b]	Coxibs	1825
23	Osteoporosis	8.5	L95[a]	Osteoporosis	1825
			M05[b]	Drugs for treatment of bone diseases	1825
24	Neurologic symptoms	2.3	N01[a]	Headache	183
			N04[a]	Restless legs	183
			N05[a]	Tingling fingers/feet/toes	183

Deficit	Deficit name	Deficit prev.	Code[a]	Description	Days[c]
			N06[a]	Sensation disturbance other	183
			N19[a]	Speech disorder	183
25	Neurologic disease	10.6	N86[a]	Multiple sclerosis	1825
			N87[a]	Parkinsonism, Parkinson's disease	1825
			N88[a]	Epilepsy	1825
			N89[a]	Migraine	1825
			N93[a]	Carpal tunnel syndrome	1825
			N94[a]	Peripheral neuritis/neuropathy	1825
			N03[b]	Antiepileptica	1825
			N04[b]	Anti-parkinson drugs	1825
26	Mood symptoms	6.1	P01[a]	Feeling anxious/nervous/tense	183
			P03[a]	Feeling depressed	183
			P05[a]	Senility, feeling/behaving old	183
27	Sleep disturbance	11.6	P06[a]	Sleep disturbance	183
			N05C[b]	Hypnotics and sedatives	183
			Med	melatonin OR valerian	183
28	Substance abuse	8.3	P15[a]	Chronic alcohol abuse	1825
			ALCO[d]	Alcohol use > 2 EH/day	1825
			P18[a]	Medication abuse	1825
			N07B[b]	Drugs used in substance abuse	1825
			P17[a]	Tobacco abuse	1825
			ROOK[d]	Smoking (1 = positive; 3 or 4 = negative)	1825
			RSTO[d]	Stop date smoking (if any RSTO date registered without a later date of P17 or ROOK, then consider P17 and ROOK as negative)	1825
			ROJN[d]	Number of years not smoking (if any ROJN date registered without a later date of P17 or ROOK, then consider P17 and ROOK as negative)	1825
			SRDA[d]	Stopped smoking since (if any SRDA date registered without a later date of P17 or ROOK, then consider P17 and ROOK as negative.)	1825
29	Cognitive impairment	5.1	P20[a]	Memory / concentration / orientation disturbance	183
			P70[a]	Dementia / Alzheimer's disease	1825

Deficit	Deficit name	Deficit prev.	Code[a]	Description	Days[c]
			P71[a]	Organic psychosis other	1825
			P73[a]	Affective psychosis	1825
			N05A[b]	Antipsychotics	1825
			N06D[b]	Anti-dementia medications	1825
30	Anxiety disorder	20.5	P74[a]	Anxiety disorder/anxiety state	1825
			N05B[b]	Anxiolytics	1825
31	Depression	12.8	P76[a]	Depressive disorder	1825
			N06A[b]	Antidepressants	1825
32	Respiratory tract symptoms	13.1	R02[a]	Shortness of breath/dyspnoea w/o K02	183
			R05[a]	Cough	183
			R06[a]	Nose bleed/epistaxis	183
			R08[a]	Nose symptom/complaint other	183
			R21[a]	Throat symptom/complaint	183
			R05[b]	Cough and cold preparations	183
			R01[b]	Nasal preparations	183
33	Respiratory infection	6.4	R74[a]	Upper respiratory infection acute	183
			R75[a]	Sinusitis acute/chronic	183
			R78[a]	Acute bronchitis/bronchiolitis	183
			R81[a]	Pneumonia	183
34	COPD /Asthma	21.4	R91[a]	Chronic bronchitis / bronchiectasis	1825
			R95[a]	Chronic obstructive pulmonary disease	1825
			R96[a]	Asthma	1825
			R03[b]	Drugs for obstructive airway diseases	1825
35	Skin symptoms	4.8	S02[a]	Pruritus	183
			S04[a]	Lump/swelling localized	183
			S06[a]	Rash localized	183
			S10[a]	Boil/carbuncle	183
			S20[a]	Corn/callosity	183
			S21[a]	Skin texture symptom/complaint	183
36	Skin infections	9.2	S03[a]	Warts	183
			S70[a]	Herpes zoster	183
			S74[a]	Dermatophytosis	183
			S75[a]	Moniliasis/candidiasis	183
			S76[a]	Skin infection other	183
			D01[b]	Antifungals for dermatological use	183

Deficit	Deficit name	Deficit prev.	Code[a]	Description	Days[c]
			D06[b]	Antibiotics and chemotherapeutics for dermatological use	183
37	Eczema, Psoriasis	37.0	S87[a]	Dermatitis / atopic eczema	1825
			S88[a]	Dermatitis / contact/allergic	1825
			S91[a]	Psoriasis	1825
			D05[b]	Antipsoriatics	1825
			D07[b]	Corticosteroids, dermatological preparations	1825
38	Skin ulcus / other skin disease	10.7	S97[a]	Chronic ulcer skin	1825
			S99[a]	Skin disease, other	1825
			Med	ulcer OR ulcus	1825
39	Intake / weight problems - nutritional deficiencies	18.2	T03[a]	Loss of appetite	183
			T11[a]	Dehydration	183
			T82[a]	Obesity	1825
			T83[a]	Overweight	1825
			T91[a]	Vitamin/nutritional deficiency	183
			T08[a]	Weight loss	183
			A11[b]	Vitamins	183
			A12[b]	Mineral supplements	183
			GEW[d]	Weight < 50 kg or > 90 kg	183
			QUET[d]	BMI index < 18.5 kg / m^2 OR ≥ 25 kg/m^2	183
			Med	enlive OR ensini OR ensure OR forti OR fresub OR fresubin OR modifast OR nutri prosure OR provide OR resource	183
40	Thyroid disorders	6.8	T85[a]	Hyperthyroidism/thyrotoxicosis	1825
			T86[a]	Hypothyroidism/myxoedema	1825
			H03[b]	Thyroid therapy	1825
			TSH[d]	Thyroid stimulating hormone < 0.35 mU/L OR > 5.5 mU/L	1825
41	Diabetes mellitus	20.4	T90[a]	Diabetes mellitus	1825
			A10[b]	Drugs used in diabetes	1825
			GLUC[d]	Venous glucose measurement > 6.4 mmol/L	1825
42	Gout	4.6	T92[a]	Gout	1825
			M04[b]	Antigout preparations	1825
43	Lipid disorders	36.9	T93[a]	Lipid disorder	1825
			C10[b]	Lipid modifying agents	1825

Deficit	Deficit name	Deficit prev.	Code[a]	Description	Days[c]
			CHOL	Total cholesterol measurement ≥ 6.5 mmol/L	1825
			HDL	HDL-cholesterol measurement <0.9 mmol/L (male) OR <1.1 mmol/L (female)	1825
			TRIG	Triglycerides measurement ≥ 2.2 mmol/L	1825
			LDL	LDL-cholesterol measurement ≥ 4.5 mmol/L	1825
44	Urinary incontinence	12.4	U04[a]	Incontinence urine	1825
			Med	tena OR abena OR abri-flex OR abri-soft OR abs OR absor OR absorin OR aichner OR att OR attends OR (cath[a] NOT (iv OR intraveneus OR intraven)) OR depend OR incont[a] OR kyl OR kylie OR molicare OR molif OR molim OR molimed OR molinea OR pois OR poise OR seni OR suprima OR wellsana	1825
			G04BD[b]	Drugs used for urinary frequency and incontinence	1825
45	Other urinary tract symptoms	4.7	U02[a]	Urinary frequency/urgency	183
			U05[a]	Urination problems other	183
			U06[a]	Haematuria	183
			U29[a]	Urinary symptom/complaint other	183
			Y06[a]	Prostate symptom/complaint	183
46	Urinary tract infection	5.1	U71[a]	Cystitis/urinary infection other	183
47	Other urinary tract disease	15.4	U95[a]	Urolithiasis	1825
			U99[a]	Urinary disease, other	1825
			KREM[d]	Glomerular filtration rate according to MDRD formula < 90 ml/min/1.73 m^2 (male) OR 80 ml/min/1.73 m^2 (female)	1825
48	Reproductive tract problems	19.2	X87[a]	Uterovaginal prolapse	1825
			Y07[a]	Impotence NOS	1825
			Y85[a]	Benign prostatic hypertrophy	1825
			G01[b]	Gynecological antiinfectives and antiseptics	183
			G03[b]	Sex hormones and modulators of the genital system	1825
			G04BE[b]	Drugs used in erectile dysfunction	1825

Deficit	Deficit name	Deficit prev.	Code[a]	Description	Days[c]
			G04C[b]	Drugs used in benign prostatic hypertrophy	1825
			SKST[d]	Sexual disfunctioning (if 1, then score positive, if 2, 8 or unknown then score negative)	1825
			Med	pess OR pessarium	1825
49	Social problems	7.2	Z01[a]	Poverty / financial problem	1825
			Z03[a]	Housing / neighbourhood problem	1825
			Z04[a]	Social cultural problem	1825
			Z10[a]	Health care system problem	1825
			Z11[a]	Compliance / being ill problem	1825
			Z12[a]	Relationship problem with partner	1825
			Z13[a]	Partner's behaviour problem	1825
			Z14[a]	Partner illness problem	1825
			Z15[a]	Loss/death of partner problem	1825
			Z16[a]	Relationship problem with child	1825
			Z18[a]	Illness problem with child	1825
			Z19[a]	Loss / death of child problem	1825
50	Medication in chronic use	24.2	All ATC-codes[b]	5 or more medications in chronic use ((chronic use is defined as 'chronisch' variable = ja) OR (herhaling >=2) OR (3 or more prescriptions in past year, of which at least 1 prescription in last 6 months))	365

[a] ICPC-codes translated from the Dutch ICPC-1 version as currently used in general practices. [b] Medication registered with ATC-codes. Med = Prescriptions registered without ATC-codes and searched by means of key words in the written prescription in the EMR. These prescriptions refer to different therapeutics, such as medications, therapeutic aids, bandages, incontinence materials, and nutritional supplements. [c] The number of days indicates the observation period counting back from the baseline date of 1 January 2008, in which the presence of an item is considered. [d] Diagnostic measurements. Criteria are given for a positive score on the particular item. prev. = prevalence.

Appendix 2. Geriatric events, psychosocial Events, and chronic diseases and impairments

Geriatric events

Item	Name	Prev	Code[a]	Description	Days[c]
1	Instability/ immobility	14.5	A06[a]	Fainting/syncope	91
			A10[a]	Bleeding-haemorrhage NOS	91
			A28[a]	Limited function/disability NOS	91
			A80[a]	Trauma/injury NOS	91
			H82[a]	Vertiginous syndrome / labyrinthitis	91
			K88[a]	Postural hypotension	91
			L02[a]	Back symptom/complaint	91
			L03[a]	Low back symptom/complaint without radiating pain	91
			L13[a]	Hip symptom/complaint	91
			L14[a]	Leg/thigh symptom/complaint	91
			L15[a]	Knee symptom/complaint	91
			L16[a]	Ankle symptom/complaint	91
			L17[a]	Foot/toe symptom/complaint	91
			L28[a]	Limited function/disability	91
			L72[a]	Fracture: radius/ulna	91
			L73[a]	Fracture: tibia/fibula	91
			L74[a]	Fracture: hand/foot bone	91
			L75[a]	Fracture: femur	91
			L76[a]	Fracture: other	91
			L77[a]	Sprain/strain of ankle	91
			L78[a]	Sprain/strain of knee	91
			L79[a]	Sprain/strain of joint NOS	91
			L80[a]	Dislocation/subluxation	91
			L81[a]	Injury musculoskeletal NOS	91
			L86[a]	Low back symptom/complaint with radiating pain	91
			L96[a]	Acute internal damage knee	91
			N17[a]	Vertigo/dizziness	91
			N18[a]	Paralysis/weakness	91
			N79[a]	Concussion	91

Item	Name	Prev	Code[a]	Description	Days[c]
			N80[a]	Head injury other	91
			S16[a]	Bruise/contusion	91
			S17[a]	Abrasion/scratch/blister	91
			S18[a]	Laceration/cut	91
			S19[a]	Skin injury other	91
			N07C[b]	Antivertigo drugs	91
			Med	decubitus	91
			Med	Wound[a] OR stitch[a] OR sling	91
2	Cognitive impairment	2.5	P20[a]	Memory / concentration / orientation disturbance	91
			P70[a]	Dementia / Alzheimer's disease	91
			P71[a]	Organic psychosis other	91
			P73[a]	Affective psychosis	91
			N05A[b]	Antipsychotics	91
			N06D[b]	Anti-dementia medications	91
3	Urinary incontinence	4.1	U04[a]	Incontinence urine	91
			Med	tena OR abena OR abri-flex OR abri-soft OR abs OR absor OR absorin OR aichner OR att OR attends OR (cath[a] NOT (iv OR intraveneus OR intraven)) OR depend OR incont[a] OR kyl OR kylie OR molicare OR molif OR molim OR molimed OR molinea OR pois OR poise OR seni OR suprima OR wellsana	91
			G04BD[b]	Drugs used for urinary frequency and incontinence	91

[a] ICPC-codes translated from the Dutch ICPC-1 version as currently used in general practices. [b] Medication registered with ATC-codes. Med = Prescriptions registered without ATC-codes and searched by means of key words in the written prescription in the EMR. These prescriptions refer to different therapeutics, such as medications, therapeutic aids, bandages, incontinence materials, and nutritional supplements. [d] Diagnostic measurements. Criteria are given for a positive score on the particular item. [c] The number of days indicates the observation period counting back from the baseline date of 1 January 2008, in which the presence of an item is considered. prev. = prevalence

Psychosocial Events

Item	Name	Prev	Code[a]	Description	Days[c]
1	Mood symptoms/ disorders	13.1	P01[a]	Feeling anxious/nervous/tense	91
			P03[a]	Feeling depressed	91
			P05[a]	Senility, feeling/behaving old	91
			P74[a]	Anxiety disorder/anxiety state	91
			N05B[b]	Anxiolytics	91
			P76[a]	Depressive disorder	91
			N06A[b]	Antidepressants	91
2	Social problems	1.4	Z01[a]	Poverty / financial problem	91
			Z03[a]	Housing / neighbourhood problem	91
			Z04[a]	Social cultural problem	91
			Z10[a]	Health care system problem	91
			Z11[a]	Compliance / being ill problem	91
			Z12[a]	Relationship problem with partner	91
			Z13[a]	Partner's behaviour problem	91
			Z14[a]	Partner illness problem	91
			Z15[a]	Loss/death of partner problem	91
			Z16[a]	Relationship problem with child	91
			Z18[a]	Illness problem with child	91
			Z19[a]	Loss / death of child problem	91

[a] ICPC-codes translated from the Dutch ICPC-1 version as currently used in general practices. [b] Medication registered with ATC-codes. Med = Prescriptions registered without ATC-codes and searched by means of key words in the written prescription in the EMR. These prescriptions refer to different therapeutics, such as medications, therapeutic aids, bandages, incontinence materials, and nutritional supplements. [d] Diagnostic measurements. Criteria are given for a positive score on the particular item. [c] The number of days indicates the observation period counting back from the baseline date of 1 January 2008, in which the presence of an item is considered. prev. = prevalence

Chronic Diseases and Impairments

Item	Name	Prev	Code[a]	Description	Days[c]
1	Cancer	11.6	A79[a]	Malignancy NOS	1825
			B72[a]	Hodgkin's disease	1825
			B73[a]	Leukaemia	1825
			B74[a]	Malignant neoplasm blood other	1825
			D74[a]	Malignant neoplasm stomach	1825
			D75[a]	Malignant neoplasm colon/rectum	1825
			D76[a]	Malignant neoplasm pancreas	1825
			D77[a]	Malig. neoplasm digest other/NOS	1825
			F74[a]	Neoplasm of eye/adnexa	1825
			H75[a]	Neoplasm of ear	1825
			K72[a]	Neoplasm cardiovascular	1825
			L71[a]	Malignant neoplasm musculoskeletal	1825
			N74[a]	Malignant neoplasm nervous system	1825
			R84[a]	Malignant neoplasm bronchus/lung	1825
			S77[a]	Malignant neoplasm of skin	1825
			T71[a]	Malignant neoplasm thyroid	1825
			U75[a]	Malignant neoplasm of kidney	1825
			U76[a]	Malignant neoplasm of bladder	1825
			U77[a]	Malignant neoplasm urinary other	1825
			X75[a]	Malignant neoplasm cervix	1825
			X76[a]	Malignant neoplasm breast female	1825
			X77[a]	Malignant neoplasm genital other (f)	1825
			Y77[a]	Malignant neoplasm prostate	1825
			Y78[a]	Malignant neoplasm male genital / mammae	1825
			L01[b]	Antineoplastic agents	1825
			L02[b]	hormonal agents given in malignant conditions	1825
2	Ischemic heart disease	16.8	K74[a]	Angina pectoris	1825
			K75[a]	Acute myocardial infarction	1825
			K76[a]	Other / chronic ischaemic heart disease	1825
			C01DA[b]	Organic nitrates	1825
3	Heart failure	5.6	K77[a]	Heart failure	1825

Item	Name	Prev	Code[a]	Description	Days[c]
4	TIA/CVA	6.6	K89[a]	Transient cerebral ischaemia	1825
			K90[a]	Stroke/cerebrovascular accident	1825
5	Arthritis/ Osteoarthrosis	21.3	L84[a]	Arthrosis/spondylosis back	1825
			L88[a]	Rheumatoid arthritis / related condition	1825
			L89[a]	Osteoarthrosis of hip	1825
			L90[a]	Osteoarthrosis of knee	1825
			L91[a]	Osteoarthrosis other / related condition	1825
			M01AH[b]	Coxibs	1825
6	COPD /Asthma	21.4	R91[a]	Chronic bronchitis / bronchiectasis	1825
			R95[a]	Chronic obstructive pulmonary disease	1825
			R96[a]	Asthma	1825
			R03[b]	Drugs for obstructive airway diseases	1825
7	Diabetes mellitus	20.4	T90[a]	Diabetes mellitus	1825
			A10[b]	Drugs used in diabetes	1825
			GLUC[d]	Venous glucose measurement > 6.4 mmol/L	1825
8	Visual impairment	11.2	F83[a]	Retinopathy	1825
			F84[a]	Macular degeneration	1825
			F92[a]	Cataract	1825
			F93[a]	Glaucoma	1825
			F94[a]	Blindness	1825
			S01E[b]	Antiglaucoma preparations and miotics	1825
9	Hearing impairment	5.0	H84	Presbyacusis	1825
			H86	Deafness	1825

[a] ICPC-codes translated from the Dutch ICPC-1 version as currently used in general practices. [b] Medication registered with ATC-codes. Med = Prescriptions registered without ATC-codes and searched by means of key words in the written prescription in the EMR. These prescriptions refer to different therapeutics, such as medications, therapeutic aids, bandages, incontinence materials, and nutritional supplements.
[d] Diagnostic measurements. Criteria are given for a positive score on the particular item. [c] The number of days indicates the observation period counting back from the baseline date of 1 January 2008, in which the presence of an item is considered. prev. = prevalence

Appendix 3. Reclassification tables of Model 2 and Model 3 compared to Model 1

Table 1. Reclassification table of model 2 compared to model 1 for risk of adverse health outcomes at one year.

	Risk according to model 2							
Risk according to	Patients with adverse health outcomes				Patients without adverse health outcomes			
model 1	Low	Medium	High	Total	Low	Medium	High	Total
Low	28 (82)	6 (18)	0 (0)	34	4159 (94)	279 (6)	0 (0)	4438
Medium	4 (5)	65 (87)	6 (8)	75	283 (6)	3876 (88)	241 (6)	4400
High	0 (0)	4 (1)	339 (99)	343	0 (0)	234 (6)	3896 (94)	4130
Total	32	75	345	452	4442	4389	4137	12968

Figures are number of patients (%). a Patients classified in agreement according to model 1 and model 2. Of all patients with adverse health outcomes, 12 (6 + 0 + 6) are reclassified to higher risk groups, and 8 (4 + 0 + 4) to lower risk groups. For patients without adverse health outcomes, this is 520 (279 + 0 + 241) and 517 (283 + 0 + 224), respectively. Reclassification improvement is 0.9% among patients with adverse health outcomes (12-8 of 452) and -0.1% among patients without adverse health outcomes (517-520 of 12968). This results in a net reclassification improvement of 0.9 + -0.02 = 0.9%.

Table 2. Reclassification table of model 2 compared to model 1 for risk of adverse health outcomes at five years.

Risk according to model 1	Risk according to model 2							
	Patients with adverse health outcomes				Patients without adverse health outcomes			
	Low	Medium	High	Total	Low	Medium	High	Total
Low	168 (87)	25 (13)	0 (0)	193	4019 (94)	260 (6)	0 (0)	4279
Medium	21 (5)	363 (86)	38 (9)	422	266 (7)	3578 (88)	209 (5)	4053
High	0 (0)	35 (3)	1363 (98)	1398	0 (0)	203 (7)	2872 (93)	3075
Total	189	423	1401	2013	4285	4041	3081	11407

Figures are number of patients (%). a Patients classified in agreement according to model 1 and model 2. Of all patients with adverse health outcomes, 63 (25 + 0 + 38) are reclassified to higher risk groups, and 56 (21 + 0 + 35) to lower risk groups. For patients without adverse health outcomes, this is 469 (260 + 0 + 209) and 469 (266 + 0 + 203), respectively. Reclassification improvement is 0.3% among patients with adverse health outcomes (63-56 of 2013) and 0% among patients without adverse health outcomes (469-469 of 11407). This results in a net reclassification improvement of 0.3 + 0 = 0.3%.

Table 3. Reclassification table of model 3 compared to model 1 for risk of adverse health outcomes at one year.

	Risk according to model 3							
Risk according	Patients with adverse health outcomes				Patients without adverse health outcomes			
to model 1	Low	Medium	High	Total	Low	Medium	High	Total
Low	23 (68)	11 (32)	0 (0)	34	4026 (91)	407 (9)	5 (0)	4438
Medium	3 (4)	48 (64)	24 (32)	75	421 (10)	3598 (82)	381 (9)	4400
High	0 (0)	4 (1)	339 (99)	343	0 (0)	406 (10)	3724 (90)	4130
Total	26 (6)	63 (14)	363	452	4447	4411 (34)	4110	12968

Figures are number of patients (%). [a] Patients classified in agreement according to model 1 and model 3. Of all patients with adverse health outcomes, 35 (11 + 0 + 24) are reclassified to higher risk groups, and 7 (3 + 0 + 4) to lower risk groups. For patients without adverse health outcomes, this is 793 (407 + 5 + 381) and 827 (421 + 0 + 406), respectively. Reclassification improvement is 6.2% among patients with adverse health outcomes (35-7 of 452) and 0.3% among patients without adverse health outcomes (827-793 of 12968). **This results in a net reclassification improvement of 6.2 + 0.3 = 6.5%.**

Table 4. Reclassification table of Model 3 compared to Model 1 for risk of adverse health outcomes at five years.

Risk according to model 1	Risk according to model 3							
	Patients with adverse health outcomes				Patients without adverse health outcomes			
	Low	Medium	High	Total	Low	Medium	High	Total
Low	156 (81)	36 (19)	1 (0)	193	3893 (91)	382 (9)	4 (0)	4279
Medium	23 (6)	306 (73)	93 (22)	422	401 (10)	3340 (82)	312 (8)	4053
High	0 (0)	47 (3)	1351 (97)	1398	0 (0)	363 (12)	2712 (88)	3075
Total	179 (9)	389	1445	2013	4294	4085	3028	11407

Figures are number of patients (%). [a] Patients classified in agreement according to model 1 and model 3. Of all patients with adverse health outcomes, 130 (36 + 1 + 93) are reclassified to higher risk groups, and 70 (23 + 0 + 47) to lower risk groups. For patients without adverse health outcomes, this is 698 (382 + 4 + 312) and 764 (401 + 0 + 363), respectively. Reclassification improvement is 3.0% among patients with adverse health outcomes (130-70 of 2013) and 0.6% among patients without adverse health outcomes (764-698 of 11407). **This results in a net reclassification improvement of 3.0 + 0.6 = 3.6%.**

Chapter 9

General discussion

Clinical case: Mr Smit

A general practitioner (GP) is on her way to see Mr Smit, a 72-year-old man, for an emergency home visit. His daughter called the GP because she found him lying on the floor, unable to stand. Before getting into her car, the GP has quickly reviewed Mr Smit's medical records: his last consultation was 10 years ago because of pneumonia, he has osteoarthrosis and mild hypertension, and wears a hearing aid. The GP remembers that Mr Smit always accompanied his wife, who passed away 14 months ago, during her frequent consultations because of severe heart failure.

At his house, the GP finds Mr Smit lying in the hallway. He is responsive; he has a pulse of 90 beats per minute, a blood pressure of 90/60 mm/Hg, and a temperature of 35.8°C. Mr Smit tells the GP that in the middle of the night, he tripped over the carpet on his way to the toilet. The GP suspects a hip fracture, and she orders an ambulance to transport Mr Smit to the hospital. Mr Smit's daughter tells the GP that she has been increasingly worried about her father. He seems depressed, has severe pain in his knees and hips, and does not eat much. The GP arranges to see Mr Smit after his hospital admission, and she wonders whether she could have done something to prevent this acute derailment.

The clinical case outlined above illustrates the current reactive delivery of primary care for older people: GPs address (semi-) acute complaints and monitor chronic diseases on an individual basis, responding to the care needs of the particular moment. This delivery makes it difficult to achieve adequate coordination of care and to support self-management; and it does not meet the long-term care needs of older patients.[1] Moreover, when patients do not consult their GPs, they are not monitored, while they could be at increased risk of adverse health outcomes. Therefore, a paradigm shift is needed from reactive care, based on responding to patients who present in individual consultations, to a proactive approach, in which primary care providers aim to monitor the health and care needs of the entire population of older patients.[2] The first step in proactive primary care is to identify frail older patients at risk.

Thesis aims

The aims of this thesis were to develop and validate U-PRIM, a screening instrument for frailty in community-dwelling older people based on routine primary care data, and to evaluate its (cost-) effectiveness when followed by regular GP care (U-PRIM intervention), or by a nurse-led proactive personalised care program (U-PRIM + U-CARE intervention).

Main conclusions from this thesis

The main conclusions of this thesis are:

- With routine primary care data from their Electronic Medical Records (EMRs), GPs can adequately predict the risk of adverse health outcomes in older people;

- A Frailty Index (FI), based on routine care data, is a valid and reliable measurement for summarising the general level of fitness or frailty of older patients in primary care;

- U-PRIM and U-PRIM followed by U-CARE result in better preservation of daily functioning in community-dwelling older people than usual care; and

- The U-PRIM + U-CARE intervention has a high probability of being cost-effective compared to usual care.

In this discussion, we will position our findings in the context of other research, elaborate on methodological challenges, and discuss implications for further research and clinical practice.

Screening for frailty based on routine primary care data

The performance of frailty screening instruments: a general overview

We demonstrated that an FI based on routine care data could adequately predict adverse health outcomes, and it was strongly correlated with other frailty instruments. In general, the performance of different frailty instruments varies widely, and so do the recommendations for practical use of these instruments.[3-8] Some studies have concluded that frailty instruments should only be used to exclude frailty.[5] Other have suggested that the specific needs of researchers, clinicians, and policy makers should determine which frailty screening tool to use.[7] Whereas the FI was identified as the best available outcome measurement of frailty in one systematic review, the 'Survey of Health, Ageing, and Retirement in Europe' (SHARE) instrument and Tilburg Frailty Indicator (TFI) were identified as the most suitable screening instruments in primary care in a second systematic review.[4,8] However, the latter two instruments include performance-based measurements and self-reported questionnaires, which limit their

use in daily practice. In a recent comparison of eight commonly used scales, the FI was considered to have high content validity, to be feasible in daily practice, and to predict all-cause mortality accurately.[3]

All FIs, although constructed with different sets and numbers of deficits, are strongly correlated with adverse health outcomes, both in the non-hospitalised older population,[9] acute surgical patients,[10] emergency department (ED) visitors,[11] and hospitalised patients.[12] Taking these findings together, we conclude that the FI concept is a valuable summary measurement of the level of fitness or frailty of older people.

The Frailty Index in the U-PROFIT trial

The FI used in the U-PRIM screening had a very restricted score distribution compared to the FIs found in other studies. This finding might have been due to the high number of missing data, i.e., information on their health status that patients have not shared with their GPs or that has not been registered appropriately in the EMR. In a revised version of the FI, for which we used additional data on symptoms, diseases, and medication, we were able to increase the upper limit of the FI score distribution to 0.70, which is comparable to other studies.[9] Scores close to that upper limit have generally been considered an alarm signal, as patients are close to severe loss of redundancy.[2] We conclude that routine care data contain sufficient information to predict adverse health outcomes.

Good quality of the data from which the FI is constructed is essential for the instrument's performance. Several studies have investigated the quality of EMR data in primary care. In a Spanish cohort study, the prevalence of multimorbidity was higher in health survey data than in EMR data, with the former being more sensitive to symptom-based conditions.[13] In the UK-based General Practice Research Database (GPRD), diagnostic coding was accurate and complete, but acute conditions were registered suboptimally.[14] The GPRD is the largest source of anonymised routine primary care data worldwide, with information on 3.6 million patients. Practices are reimbursed for their registration efforts, and the data undergo extensive quality checks. In the Netherlands, GPs use multiple EMR systems, which could contribute to increased variability in data registration. To provide greater insight into the registration quality, a regional EMR quality scan was performed among 100 general practices.[15] Although the majority of consultations were given rational ICPC codes, greater variability in the number of active episodes per patient was found, and medication was not always properly coded. We attempted to limit the impact of these quality issues by combining multiple EMR data

sources for each deficit, such as data on diagnosis and medication use, and by implementing a longer observation period.
For optimal performance of the FI we must continue working on the quality of EMR data registration. In the Netherlands, proper use of ICPC codes is stimulated by the dissemination of guidelines by the Dutch College of General Practitioners and by implementation courses.

Polypharmacy
By including polypharmacy in the U-PRIM instrument, we aimed to increase the validity of the screening instrument. As a proxy for disease burden and because of its related risk of adverse effects, polypharmacy has been strongly associated with an increased risk of adverse health outcomes.[16] By presenting it as a separate variable, GPs are alerted to the high prevalence of and associated health risks with polypharmacy. Evidence for the effects of a comprehensive medication review on direct patient-related outcomes is limited, but research has suggested that it could decrease the risk of adverse drug reactions and improve pharmaceutical care.[17]

Consultation gap
Patients who have not visited a general practice for some time might be healthy, but 'no shows' may also be a signal of care avoidance, with increased risk of adverse outcomes. For the original U-PRIM instrument we chose a cut-off value of three years, balancing between the consultation gap as a possible expression of good health and of care avoidance. However, 75% of the patients with long consultation gaps were found to have health problems requiring a GP's attention. To refine this approach further, we divided the consultation gap in three parts, in line with the observed associated risks in the prognostic model study: a low consultation gap (less than one month), associated with a medium risk; a moderate consultation gap (1-12 months), associated with the least risk of adverse health outcomes; and a long consultation gap (over 12 months), associated with the greatest risk.

The U-PROFIT trial

In the U-PROFIT trial, we demonstrated that U-PRIM followed by proactive care by the GP or by the U-CARE program resulted in a better preservation of daily functioning in community-dwelling older people compared to usual primary care. In the study, both strategies, i.e., U-PRIM and U-PRIM followed by U-CARE, showed similar effects. This finding raises the question of whether implementation of U-CARE, a resource-intensive

intervention, is warranted because of its additional benefits when compared to U-PRIM followed by regular GP care. In pre-specified subgroup analyses, the achieved effects of U-PRIM + U-CARE were substantially more pronounced than those of U-PRIM alone in the subgroup of relatively highly educated patients. We expect that over a longer observation period the added benefit of the U-CARE nurse-led proactive care program to the U-PRIM intervention would be demonstrated for the entire population of older patients.

There are two aspects that might have influenced the generalisability and interpretability of our results.

Informed consent and risk of selective inclusion

Of 7638 eligible patients, only 3092 (42%) consented to participate in the U-PROFIT trial. With the more frail and comorbid older people less likely to participate, this finding might reflect selective inclusion, which could have resulted in underestimation of the true intervention effect. The elaborate informed consent procedure, which might be difficult to understand for older patients, could also have contributed to this selective inclusion. It could be questioned whether in the U-PROFIT trial, this individual informed consent was required, as the interventions were basically organisational changes to existing primary care aimed at optimising its effectiveness. No additional interventions or additional risks were introduced. Evaluations were mainly performed using questionnaires and routine care data. Although we do underline the need for proper research conduct, we believe that in implementation research with routine care interventions, ethical review boards should more carefully consider the delicate balance between the need for individual informed consent, and the risk of inducing selective inclusion, to avoid severe limitation of the external validity of study results.

Registration of care provision in the U-PRIM intervention group

In the U-PRIM intervention group, GPs were asked to provide proactive care according to current standards and guidelines. Because we did not want to disrupt the daily routines in clinical practice, we did not ask GPs to register specifically which actions during the follow-up period were triggered by the U-PRIM report. The number of GP consultations – in the office, at home, or by telephone - did not increase in the U-PRIM intervention, compared to usual care. Therefore, either the awareness of the GPs or the focus of the consultations must have changed, or the U-PRIM report could have affected other care processes, such as medication reviews or peer consultations. These

hypotheses should be explored further, so U-PRIM can be tailored optimally to support those care processes for which GPs find it helpful to use the report.

Comparison with other studies

Studies on proactive care for frail older people have reported mixed results. Comprehensive care for older adults with multimorbidity improved at least one aspect from among care quality, efficiency, or health-related outcomes.[18] Comprehensive care, targeting specific risk factors or areas in which patients experienced difficulties, appeared to be more effective than more general organisational changes to the care process.[19] In an overview of comprehensive care specifically targeting frail older people, there was no difference between comprehensive care and usual care in 57% of the assessed outcomes; in 2%, the results were unclear; 6% were in favour of usual care; and 35% were in favour of the comprehensive care.[20] In these reviews, there was little emphasis on the possible contribution of panel management support systems. In a previous qualitative study on panel management, patients reported that they appreciated the panel management outreach, but they also noted that careful attention should be paid to the coordination of care.[21] Physicians believed that panel management improved care for their patients, but they were also apprehensive that panel management would add more tasks to their busy day. However, with the U-PROFIT trial we showed feasibility in general practice.[22] Moreover, we have made a contribution to this field, demonstrating that the empanelment of frail older people, followed by regular care or a nurse-led proactive care program is effective, and that the latter intervention is also cost-effective.

Cost-effectiveness of the U-PROFIT program

In the cost-effectiveness analysis of the U-PROFIT trial, we demonstrated that at a willingness-to-pay of € 20 000 per QALY, U-PRIM + U-CARE had a high probability of being cost-effective. This cost-effectiveness was mainly based on the substantial cost savings, while the effect differences as expressed in quality of life improvements were minimal.

The potential cost savings in the U-PRIM + U-CARE group, compared to the usual care group, are substantial and highly relevant in light of increasing healthcare costs. Between 2000 and 2011, healthcare costs more than doubled in the Netherlands from € 44 billion to € 93 billion.[23] Of the healthcare budget, 44% is spent on the healthcare of people aged 60 years and older.[24] In the U-PRIM + U-CARE group, the net annual saving for each frail older patient participating was € 684 (95% CI € -1671 to € 221) compared to

usual care. Assuming nationwide implementation of the U-PROFIT program in primary care in the Netherlands, this program could potentially result in an extrapolated savings of more than € 500 million annually. These savings would reduce the total annual healthcare budget by 0.5% and that of the care budget for older people by 1%. Of course, these potential savings are based on extrapolation, and they must be interpreted with accompanying assumptions and uncertainty. Compliance with the intervention in real-life daily practice could be lower, and the long-term effects of the U-PROFIT strategy still must be established. For nationwide implementation, the costs for reimbursement of GPs and nurses will have to be negotiated, and large-scale availability of the U-CARE educational module for practice nurses must be realised. Despite these uncertainties, we believe that the U-PROFIT intervention program is cost-effective and helps older people to maintain their daily functioning. Therefore, we recommend that insurance companies and the Health Care Insurance Board facilitate large-scale implementation of the U-PROFIT intervention strategy by incorporating it in the reimbursed care program.

Proactive primary care: ethical dilemmas and preferences of patients and caregivers

Patients might experience proactive primary care as an intrusion on their sense of autonomy. However, in one study, frail older patients stated that they welcomed unsolicited home visits by practice nurses, but expected that the focus would be on care and wellbeing, rather than on cure and prevention.[25] A second study reported that in a proactive care approach, frail older patients felt acknowledged and supported.[26] In a qualitative study embedded in the U-PROFIT trial, we demonstrated that frail older patients welcomed proactive nurse-led care when it was tailored to address individual needs.[27] Observation and assessment of potential risks were identified among nurses' most important roles. In conclusion, patients seem receptive to a proactive care approach. Primary care providers should always aim to respect and enhance patients' sense of autonomy and to consider patients' needs and backgrounds. It is also important to emphasise that proactive care not be imposed on frail older patients; rather, different options should be proactively offered, and in conjunction with their GPs, patients should decide for themselves whether to accept the offered care.

Implications for further research, education, and clinical practice

In 2012, the Dutch College of General Practitioners and the National Association of General Practitioners published a vision document on primary care in 2022.[28] In this document, the importance of the key values of primary care – a generalist approach, personalised care, and continuity of care – were emphasised. Furthermore, strengthening the coordinating role of GPs and implementation of panel management strategies were specifically mentioned.

The results presented in this thesis underline that empanelment of frail older patients, followed by proactive care, is feasible, but a number of questions remain to be evaluated. For future primary care practice, we recommend nationwide implementation of the U-PRIM instrument in combination with the U-CARE program, in primary care in the Netherlands. Based on our findings, we conclude that this implementation will help older patients to maintain their daily functioning, reduce negative health outcomes and lower the societal costs for healthcare.

In future research, the performance of the expanded prognostic models we developed should be externally validated to improve our proposed empanelment and panel management procedures further. Additionally, GPs should provide feedback regarding the optimal operationalisation of panel management in daily practice. Third, the U-PRIM tool should be further developed, from an 'empanelment' tool to a true 'panel management' tool. This development would imply that depending on patients' levels of risk, U-PRIM would provide alerts for specific follow-up actions.

As for education, the concepts of proactive population-based care should be integrated into the training of medical students and GPs, so that they will be aware of different approaches to providing proactive, tailored care to meet the complex care needs of this vulnerable patient group. Collaboration with practice nurses should be an integral part of GP training.

Clinical case revisited: a proactive panel management approach

Imagine a different approach to primary care for older people, in which the GP and his or her team have planned an afternoon for proactive panel management, revising all high-risk patients in the U-PRIM report. The GP notices that Mr Smit has a consultation gap of 10 years, and asks the practice nurse to visit Mr Smit for a CGA. Mr Smit tells the nurse that he experiences severe pain in his knees and hips, feels sad since his wife passed away, and has lost his appetite. The practice nurse screens the house for situations with high risks of falling, and Mr Smit agrees to three small carpets in the hallway being removed. The nurse also arranges for a personal alarm system, matches Mr Smit with a

volunteer who will regularly visit, and provides nutritional advice. The GP starts pain medication, refers Mr Smit to a physiotherapist, and decides together with him they will follow up on his mood before considering antidepressants. Due to this proactive care approach, the GP and practice nurse have provided optimal conditions for Mr Smit to continue to live independently with a high quality of life.

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Chapter 10

Summary

Samenvatting
Dankwoord
Curriculum vitae
List of publications

Worldwide, the proportion of older people in the population is increasing. In the Netherlands, the number of people aged 65 years or older will increase from 2 million in 2012 to 4.7 million in 2060. Many of these older people will experience a range of health problems, such as multimorbidity, disability, and loss of quality of life. The concept of frailty aims to capture those older people at highest risk of derailment. Frailty is defined as a condition characterised by decreased homeostatic reserves and diminished resistance to stressors, resulting in increased risk of adverse health outcomes.

General practitioners (GPs) play a key role in the provision and coordination of care for this increasing group of frail older patients. However, the traditional reactive approach in primary care is often inadequate. Amidst of the broad spectrum of interacting medical and social problems of frail older patients, GPs are unable to adequately monitor the health status of their older population and tend to focus on one single illness instead of maintaining a holistic view. This leads to unnecessary disease burden, avoidable acute derailments and hospitalisations, and high societal costs. Therefore, a paradigm shift is necessary in primary care for older people, from reactive care for individual patients to a more proactive care provision based on frailty risk identification among older patients.

One way to provide proactive primary care for older people is by so-called 'panel management', in which GPs and other primary care providers, such as practice nurses, proactively identify and address care needs, based on risk identification in the patient population. Currently, there is no consensus on how to adequately identify frailty in the population of older patients. Frailty could be operationalised by means of performance-based instruments, questionnaires, or tools relying on clinical judgment. However, the first category requires extra time and resources to be completed; the second comes with a risk of non-response; and the latter requires the patient to be present for an appropriate clinical assessment, which are all considerable drawbacks for implementation in daily clinical practice. A fourth operationalisation of frailty is defined by the Frailty Index (FI), which considers frailty as an accumulation of health deficits, such as symptoms, diseases, and impairments. Out of a predefined list, the proportion of deficits present in a patient is the resulting FI score. Software-based screening of routine care data from GPs electronic medical records (EMRs) could facilitate efficient application of the FI in frailty screening in older people, without the necessity to gather additional data. Such a frailty screening strategy could also incorporate other routine care data, such as data on medication use and consultation intervals. However, so far, there is no evidence for the effectiveness of EMR-based frailty screening of older people in primary care.

In this thesis, our aims were to develop and validate U-PRIM, a screening instrument for frailty in community-dwelling older people based on routine primary care data, and to evaluate its (cost-) effectiveness with screening embedded in regular GP care (U-PRIM intervention) or when followed by a structured nurse-led proactive personalised care intervention (U-CARE).

In **chapter 2**, we describe the design of the U-PROFIT trial, in which we evaluate the effectiveness of U-PRIM embedded in regular GP care, and U-PRIM followed by U-CARE, on the level of daily functioning of community-dwelling frail older people compared to usual care. We designed a three-armed, cluster randomised single blind controlled trial in 39 clusters of general practices. We discuss our approach to several methodological challenges in the U-PROFIT trial, such as a modified informed consent procedure to prevent selective inclusion and loss to follow-up, and various retention strategies, e.g., phone calls and home visits, to limit loss to follow-up.

In **chapter 3**, we focus on the FI component of the U-PRIM instrument. In a retrospective cohort study with 2 year follow-up in one large primary care center, we investigated whether an FI based on ICPC encoded routine care data out of GPs EMRs can predict the risk of adverse health outcomes in community-dwelling older people. When the patient population (n = 1679) was divided in three groups based on FI score, we demonstrated that FI tertiles were able to discriminate between low, intermediate and high risk of adverse health outcomes. Corrected for age, consultation gap, and sex, the FI score was associated with an increased risk for emergency department (ED) and after-hours GP visits, nursing home admission, and death. The FI had a moderate predictive ability for these adverse health outcomes.

To further explore the FI component of the U-PRIM instrument, we performed a systematic review of its psychometric properties in **chapter 4**. In general, the FI showed good criterion and construct validity, but studies on responsiveness were lacking. Compared to studies using data gathered for research purposes, the FI score distribution was markedly limited in our own study using routine primary care data. We concluded that the FI is a valid frailty screening tool, but further research is needed to investigate on the generalisability of the psychometric properties of the FI to a primary care setting.

In **chapter 5**, we examined whether an FI based on ICPC encoded primary care data and the Groningen Frailty Indicator (GFI) questionnaire identified the same older people as frail. In a cross-sectional, observational study of 1580 patients, we demonstrated that there was a positive correlation between the FI and GFI. When evaluating dichotomised scores, the majority of patients with a low FI score also had a low GFI questionnaire

score. However, in patients with a high FI score, just over half of patients also had a high GFI questionnaire score. A continuous FI score accurately predicted a dichotomised GFI questionnaire score. We concluded that the FI and GFI questionnaire only moderately overlap in identifying frailty in community-dwelling older patients, and suggest a two-step frailty screening process in primary care: initial FI screening in routine healthcare data, followed by a GFI questionnaire for those with a high FI score or otherwise at high risk.

In **chapter 6**, we present the results of the U-PROFIT trial. Overall, patients in both the U-PRIM and U-PRIM + U-CARE intervention groups demonstrated better preservation of daily functioning compared to patients in the usual care group. Higher educational level positively affected outcomes for patients in the U-PRIM + U-CARE group, indicating that the U-CARE effect is dependent on individual patient characteristics, and that the nurse-led proactive care program should be further tailored to meet the needs of the heterogeneous group of frail older people. No differences in quality of life were found. Patients in the U-PRIM + U-CARE group consulted their general practice more often than patients in the other two groups.

In **chapter 7**, we discuss the cost-effectiveness analysis of the results of the U-PROFIT trial. For both the U-PRIM and U-PRIM + U-CARE group, the total costs per patient during the follow-up year were lower than for patients in the control group. At a willingness-to-pay of € 20 000 per quality adjusted life year (QALY), the U-PRIM intervention alone had a low probability of being cost-effective, and the U-PRIM + U-CARE intervention had a high probability of being cost-effective compared with usual care. Combined with the clinical findings from the U-PROFIT trial, we recommend implementation of the U-PRIM + U-CARE intervention for proactive primary care for frail, community-dwelling older people.

In **chapter 8**, based on our previously developed U-PRIM instrument, we evaluated prognostic models based on routine care data out of GPs EMRs to further improve risk assessment in frail older people, both in a population-based approach and during individual consultations. In a prognostic cohort study with a five-year follow-up period of 13 420 patients aged 60 years and older, we demonstrated that the refined models were able to adequately predict the risk of nursing home admission and death in community-dwelling older people. The most elaborate model, including age, sex, polypharmacy, consultation gap, frailty index, geriatric events, psychosocial events, and chronic diseases and impairments demonstrated a superior performance. This model could be used as an automated screening tool embedded in the EMR for proactive population-

based care, whereas a prediction rule we derived from a simplified model could be used for case-finding of frailty during individual consultations.

In **chapter 9**, we position our findings in the context of other research, elaborate on methodological challenges, and discuss implications for further research and clinical practice. We conclude that the FI concept is a valuable summary measurement of the level of fitness or frailty of older people. The quality of EMR data registration is of vital importance for optimal performance of the FI.

Regarding the U-PROFIT trial, we highlight two important issues. First, selective inclusion might have resulted in underestimation of the true intervention effect. Second, regarding the positive effect of the UPRIM report, we hypothesise that the awareness of the GPs or the focus in the consultations must have changed. These hypotheses should be explored further.

Regarding the cost-effectiveness analysis, we point out that high probability of cost-effectiveness of U-PRIM + U-CARE compared to usual care is mainly based on the cost savings in secondary care, which is highly relevant in light of the increasing healthcare costs. Of the healthcare budget of € 93 billion, 44% is spent on healthcare of people aged 60 years and older. Extrapolating the net annual savings in the U-PRIM + U-CARE group from a healthcare perspective, this could potentially lead to a 0.5% decrease in the total annual healthcare costs. However, this extrapolation must be interpreted with caution due to the accompanying uncertainties.

In conclusion, we recommend large-scale nationwide implementation of the U-PROFIT intervention strategy in primary care In future research, the refined prognostic models we developed in chapter 8 should be externally validated; GPs should provide feedback on the optimal operationalisation of panel management in daily practice; and the U-PRIM instrument should be further developed, from an 'empanelment' tool to a true panel management tool. Furthermore, the concepts of proactive population-based care should be integrated into the training of medical students, GPs, and practice nurses, so that they will be aware of different approaches to provide proactive, tailored care to meet the complex care needs of frail older people.

Chapter 10

Summary

Samenvatting

Dankwoord
Curriculum vitae
List of publications

Wereldwijd neemt het aandeel ouderen in de populatie toe. In Nederland zal het aantal mensen van 65 jaar en ouder toenemen van 2 miljoen in 2012 tot 4,7 miljoen in 2060. Veel van deze ouderen zullen met verschillende gezondheidsproblemen te maken krijgen, zoals multimorbiditeit, beperkingen, en verlies van kwaliteit van leven. Kwetsbare ouderen lopen het hoogste risico op deze ontsporingen. Kwetsbaarheid wordt gekarakteriseerd door verminderde homeostatische reserves en een verminderde weerstand tegen stressoren, wat resulteert in een verhoogd risico op negatieve gezondheidsuitkomsten.

Huisartsen spelen een belangrijke rol in het bieden en coördineren van zorg voor deze steeds groter wordende groep van kwetsbare ouderen. De traditionele reactieve benadering in de huisartsenzorg is echter vaak niet voldoende. Door het brede spectrum aan samenhangende medische en sociale problemen lukt het huisartsen niet altijd om de gezondheidsstatus van hun kwetsbare oudere populatie adequaat te monitoren. Huisartsen focussen zich in de praktijk vaak op één ziekte tegelijk, in plaats van een holistische blik te behouden. Dit leidt tot onnodige ziektelast, vermijdbare acute ontsporingen en ziekenhuisopnames, en hoge kosten voor de samenleving. Er is daarom een transitie noodzakelijk in de huisartsenzorg, van reactieve zorg voor individuele patiënten naar meer proactieve zorg gebaseerd op identificatie van kwetsbaarheid onder oudere patiënten.

Eén methode om proactieve huisartsenzorg te bieden aan oudere patiënten is door middel van 'panel management'. Huisartsen en praktijkverpleegkundigen identificeren daarbij structureel de zorgbehoeften van de patiëntenpopulatie met verhoogd risico, de kwetsbare ouderen, prioriteren en bieden vervolgens proactieve zorg. Er is op dit moment echter geen consensus over hoe kwetsbaarheid adequaat geïdentificeerd kan worden bij oudere patiënten. Kwetsbaarheid kan gemeten worden met instrumenten waarvoor patiënten fysieke tests moeten uitvoeren, met vragenlijsten, of met instrumenten gebaseerd op een klinisch oordeel. De eerste benadering vereist echter extra tijd en middelen, de tweede heeft daarnaast een risico op non-response, en net als voor de eerste benadering is het voor de derde benadering noodzakelijk dat patiënten fysiek aanwezig zijn. Dit zijn allemaal nadelen die implementatie van deze instrumenten in de praktijk kunnen beperken. In de vierde benadering wordt kwetsbaarheid opgespoord aan de hand van de Frailty Index (FI). De FI ziet kwetsbaarheid als een opeenstapeling van gezondheidsdeficits, zoals ziekten, symptomen en beperkingen. Van een vooraf gedefinieerde lijst met gezondheidsdeficits is de proportie van aanwezige deficits de resulterende FI score van een patiënt. Screening van routinezorgdata uit het Huisartsen Informatie Systeem (HIS) met behulp van een software-applicatie zou

efficiënte toepassing van de FI in het screenen op kwetsbaarheid van oudere patiënten kunnen faciliteren, zonder de noodzaak om aanvullende data te moeten verzamelen. In die screening op kwetsbaarheid kunnen ook andere routinezorgdata gebruikt worden, zoals data over medicatiegebruik en consultatie-intervallen. Er is echter tot dusver geen bewijs voor de effectiviteit van op routinezorgdata gebaseerde screening op kwetsbaarheid van oudere patiënten in de huisartsenpraktijk.

In dit onderzoek waren onze doelen om de U-PRIM, een screeningsinstrument voor kwetsbaarheid onder thuiswonende ouderen gebaseerd op routinezorgdata, te ontwikkelen en valideren, en om de (kosten)effectiviteit van de U-PRIM te onderzoeken wanneer het instrument gevolgd werd door reguliere huisartsenzorg, dan wel door een structureel proactief verpleegkundig zorgprogramma (U-CARE).

In **hoofdstuk 2** beschrijven we het design van de U-PROFIT trial, waarin we de effectiviteit van U-PRIM gevolgd door reguliere huisartsenzorg, en U-PRIM gevolgd door U-CARE op het niveau van dagelijks functioneren van kwetsbare ouderen in de huisartsenpraktijk onderzoeken, vergeleken met de gebruikelijke zorg. Hiervoor hebben we een drie-armige, clustergerandomiseerde, enkel geblindeerde gecontroleerde trial opgezet in 39 clusters van huisartsenpraktijken met één jaar follow-up. We bespreken enkele methodologische uitdagingen van de U-PROFIT trial, zoals de modified informed consent procedure om selectieve inclusie en uitval te voorkomen, en verschillende strategieën om zoveel mogelijk patiënten in de studie te behouden, zoals nabellen en huisbezoeken.

In **hoofdstuk 3** evalueren we de FI component van het U-PRIM instrument. In een retrospectieve cohortstudie met twee jaar follow-up in een groot gezondheidscentrum, hebben we onderzocht of een FI gebaseerd op ICPC-gecodeerde routinezorggegevens uit het HIS het risico op negatieve gezondheidsuitkomsten kan voorspellen voor oudere patiënten. Met de studiepopulatie (n = 1679) verdeeld in drie groepen gebaseerd op de hoogte van de FI score, hebben we laten zien dat de tertielen van de FI discrimineren tussen een laag, gemiddeld en hoog risico op negatieve gezondheidsuitkomsten. Gecorrigeerd voor leeftijd, geslacht en consultatie-interval was de FI daarnaast ook geassocieerd met een verhoogd risico op spoedeisende hulp- en huisartsenpostbezoek, verpleeghuisopname en overlijden. De FI had een redelijk voorspellende waarde voor deze negatieve gezondheidsuitkomsten.

Om de FI component van het U-PRIM instrument verder te onderzoeken, hebben we in **hoofdstuk 4** een systematische review naar de psychometrische eigenschappen van de FI gedaan. In de 20 geïncludeerde studies liet de FI over het algemeen een goede criterion en construct validiteit zien, maar studies over responsiviteit ontbraken.

Vergeleken met studies die data gebruikten die verzameld waren voor onderzoeksdoeleinden was de FI score distributie sterk beperkt in onze eigen studie waarin routinezorggegevens zijn gebruikt. We concluderen dat de FI een valide screeningsinstrument voor kwetsbaarheid is, maar dat verder onderzoek noodzakelijk is naar de generaliseerbaarheid van de psychometrische eigenschappen van de FI naar de huisartsenpraktijk.

In **hoofdstuk 5** hebben we onderzocht of een FI gebaseerd op ICPC gecodeerde routinezorg data en de Groningen Frailty Indicator (GFI) vragenlijst dezelfde ouderen als kwetsbaar identificeerden. In een cross-sectionele, observationele studie van 1580 patiënten toonden we een positieve correlatie aan tussen de FI en GFI. Wanneer we de gedichotomiseerde scores onderzochten, dan had het grootste deel van de patiënten met een lage FI score ook een lage GFI score. In de groep patiënten met een hoge FI score had echter slechts iets meer dan de helft van de patiënten ook een hoge GFI score. Een continue FI score was een goede voorspeller voor een gedichotomiseerde GFI score. We concluderen dat de FI en GFI vragenlijst slechts beperkt overlappen in de identificatie van kwetsbaarheid bij thuiswonende oudere patiënten, en we stellen een tweetraps screeningsproces voor in de eerste lijn: een initiële screening in routinezorgdata met de FI, gevolgd door een GFI vragenlijst voor diegenen met een hoge FI score.

In **hoofdstuk 6** presenteren we de resultaten van de U-PROFIT trial, waarin 3092 patiënten zijn geïncludeerd. Patiënten in zowel de U-PRIM groep als U-PRIM + U-CARE groep lieten na een jaar een beter behoud van niveau van dagelijks functioneren zien dan patiënten die de gebruikelijke zorg ontvingen. Een hoog opleidingsniveau verbeterde de uitkomsten in de U-PRIM + U-CARE groep, wat erop wijst dat het effect van U-CARE afhankelijk is van individuele patiëntkarakteristieken en dat het verpleegkundig zorgprogramma verder ontwikkeld moet worden om aan de zorgbehoeftes van de heterogene groep van kwetsbare ouderen te voldoen. Er werd geen verschil in kwaliteit van leven gevonden. Patiënten in de U-PRIM + U-CARE groep hadden meer consulten bij hun huisartspraktijk dan patiënten in de andere twee groepen.

In **hoofdstuk 7** bespreken we de kosteneffectiviteitsanalyse van de resultaten van de U-PROFIT trial. Voor patiënten in zowel de U-PRIM groep als de U-PRIM + U-CARE groep waren de totale kosten per patiënt per jaar lager dan voor patiënten in de controlegroep. Bij een willingness-to-pay van € 20 000 per quality adjusted life year (QALY) was de kans dat de U-PRIM alleen kosteneffectief was laag, terwijl de gecombineerde U-PRIM + U-CARE interventie een grote kans had om kosteneffectief te

zijn. Gebaseerd op deze kosten- en klinische effectiviteit in de U-PROFIT trial, raden wij aan om de U-PRIM + U-CARE interventie voor proactieve zorg aan kwetsbare oudere patiënten te implementeren in de huisartsenpraktijk.

In **hoofdstuk 8** hebben we verschillende prognostische modellen geëvalueerd die gebaseerd waren op het eerder ontwikkelde U-PRIM instrument. Het doel van deze modellen, die ook gebruik maakten van routinezorggegevens uit het HIS, was om het risico-assessment in kwetsbare ouderen verder te verbeteren, zowel in een populatiebenadering als in individuele consulten. In een prognostische cohortstudie met 5 jaar follow-up van 13420 patiënten van 60 jaar en ouder, hebben we aangetoond dat de verbeterde prognostische modellen het risico op verpleeghuisopname en overlijden adequaat konden voorspellen. Het meest uitgebreide prognostische model, met daarin leeftijd, geslacht, polyfarmacie, consultatie-interval, frailty index, geriatrische events, psychosociale events, en chronische ziekten en beperkingen had de beste voorspellende waarde. Dit model zou gebruikt kunnen worden als een geautomatiseerd screeningsinstrument, ingebed in het HIS voor proactieve zorg op populatieniveau. Een predictieregel die kan worden afgeleid van een vereenvoudigd model zou gebruikt kunnen worden voor case-finding van kwetsbaarheid tijdens individuele consulten.

In **hoofdstuk 9** positioneren we onze bevindingen in de context van ander onderzoek, bespreken we methodologische uitdagingen, en gaan in op implicaties voor verder onderzoek en voor de klinische praktijk. We concluderen dat het FI concept een waardevolle en bruikbare maat is voor het niveau van kwetsbaarheid van ouderen. De kwaliteit van HIS data is van essentieel belang voor optimale performance van de FI.

We bespreken twee belangrijke punten bij de interpretatie van de U-PROFIT trial. Ten eerste kan het zo zijn dat selectieve inclusie mogelijk geresulteerd heeft in een onderschatting van het daadwerkelijke interventie-effect. Ten tweede kan het positieve effect van het aanbieden van de U-PRIM rapportage toe te schrijven zijn aan het feit dat de alertheid van de huisartsen of de inhoud van de individuele consulten is veranderd. Deze hypotheses moeten verder worden onderzocht.

We wijzen er op dat de waarschijnlijke kosteneffectiviteit van U-PRIM + U-CARE vergeleken met gebruikelijke zorg met name komt door kostenbesparingen in de tweede lijn en in het verpleeghuis, wat zeer relevant is met het oog op de toenemende kosten van de gezondheidszorg. Van het jaarlijks zorg en welzijnsbudget van € 93 miljard, wordt 44% besteed aan de zorg voor patiënten van 60 jaar en ouder. Wanneer we de netto jaarlijkse besparing per patiënt in de U-PRIM + U-CARE groep vergeleken met gebruikelijke zorg extrapoleren, dan kan dit potentieel leiden tot een jaarlijkse besparing van 0,5% op het nationale budget voor gezondheidszorg en welzijn. Deze

extrapolatie moet met medeneming van de bijkomende onzekerheidsmarges geïnterpreteerd worden.

Concluderend doen wij de aanbeveling om de U-PROFIT interventiestrategie breed te implementeren in de huisartsenpraktijk. In toekomstig onderzoek moeten de verbeterde prognostische modellen die in hoofdstuk 8 ontwikkeld zijn extern gevalideerd worden; er moet gestructureerd feedback verkregen worden van huisartsen over de optimale operationalisatie van panel management in de dagelijkse praktijk; en U-PRIM zou verder ontwikkeld moeten worden van een 'empanelment' instrument naar een daadwerkelijk panel management instrument. Daarnaast moeten de concepten van proactieve eerstelijnszorg op populatieniveau geïntegreerd worden in het onderwijs aan medisch studenten, huisartsen-in-opleiding en praktijkverpleegkundigen, zodat zij zich bewust zijn van de verschillende benaderingen om proactieve zorg te kunnen bieden om te kunnen voldoen aan de complexe zorgbehoeften van kwetsbare ouderen.

Chapter 10

Summary
Samenvatting

Dankwoord

Curriculum vitae
List of publications

Hoe vat je een promotie samen? Promoveren is aan je onderzoeksproject werken, en tegelijkertijd ook zoveel meer: samenwerken, jezelf leren kennen en durven laten zien, omgaan met pieken en dalen, je grenzen vormgeven, een boodschap leren overbrengen, en ontdekken wat je inspireert en motiveert. In de afgelopen vier jaar heb ik in het Om U project met veel mensen mogen werken die hierin, en in vele andere dingen, een belangrijke rol hebben gespeeld. Ik wil hen hier graag bedanken.
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Chapter 10

Summary
Samenvatting
Dankwoord

Curriculum vitae

List of publications

Curriculum vitae

Irene Drubbel was born on February 27th, 1983 in Hilversum, the Netherlands. After graduating cum laude from the Gymnasium at the Alberdingk Thijm College in Hilversum, she started medical school at the University of Utrecht. In her sixth year, she collaborated on an annual report of Cystic Fibrosis patients, under supervision of Prof. Dr. C.K. van der Ent (University Medical Center Utrecht). She obtained her medical degree in 2006, after which she worked as a resident in intensive care, paediatrics, and internal medicine, consecutively.

In 2009, Irene started working on the research described in this thesis, under supervision of Prof. Dr. N.J. de Wit (Julius Center for Health Sciences and Primary Care), Prof. Dr. M.E. Numans (Julius Center for Health Sciences and Primary Care), and Prof. Dr. M.J. Schuurmans (Department of Rehabilitation, Nursing Science, and Sport at the University Medical Center Utrecht). She will obtain her Master of Science degree in Clinical Epidemiology at the University of Utrecht in 2014. In March 2014, she will start the GP specialty training at the Department of General Practice of the Julius Center in Utrecht. Irene lives together with Pedro Rodrigues, and together they have a son: Diogo (2012).

Chapter 10

Summary
Samenvatting
Dankwoord
Curriculum vitae

List of publications

List of publications

1. Bleijenberg N, **Drubbel I**, Ten Dam VH, Numans ME, Schuurmans MJ, de Wit NJ. Proactive and integrated primary care for frail older people: design and methodological challenges of the Utrecht primary care PROactive frailty intervention trial (U-PROFIT). BMC Geriatr. 2012 Apr 25;12:16.

2. **Drubbel I**, de Wit NJ, Bleijenberg N, Eijkemans RJ, Schuurmans MJ, Numans ME. Prediction of adverse health outcomes in older people using a frailty index based on routine primary care data. J Gerontol A Biol Sci Med Sci. 2013 Mar;68(3):301-8.

3. **Drubbel I**, Bleijenberg N, Kranenburg G, Eijkemans RJ, Schuurmans MJ, de Wit NJ, Numans ME. Identifying frailty: do the Frailty Index and Groningen Frailty Indicator cover different clinical perspectives? a cross-sectional study. BMC Fam Pract. 2013 May 21;14:64

4. Bleijenberg N, Ten Dam VH, **Drubbel I**, Numans ME, de Wit NJ, Schuurmans MJ. Development of a Proactive Care Program (U-CARE) to Preserve Physical Functioning of Frail Older People in Primary Care. J Nurs Scholarsh. 2013 Sep;45(3):230-7.

5. Bleijenberg N, Ten Dam VH, Steunenberg B, **Drubbel I**, Numans ME, De Wit NJ, Schuurmans MJ. Exploring the expectations, needs and experiences of general practitioners and nurses towards a proactive and structured care programme for frail older patients: a mixed-methods study. J Adv Nurs. 2013 Oct;69(10):2262-73.

6. ten Dam VH, Bleijenberg N, Numans ME, **Drubbel I**, Schuurmans MJ, de Wit NJ. Proactive and structured care for the elderly in primary care. Tijdschr Gerontol Geriatr. 2013 Apr;44(2):81-9.

7. Laan W, Bleijenberg N, **Drubbel I**, Numans ME, de Wit NJ, Schuurmans MJ. Factors associated with increasing functional decline in multimorbid independently living older people. Maturitas. 2013 Jul;75(3):276-81.

8. Laan W, Zuithoff PA, **Drubbel I**, Bleijenberg N, Numans ME, Schuurmans MJ, de Wit NJ. Validity and reliability of the Katz-15 scale to measure unfavorable health outcomes in community-dwelling older people. The Journal of Nutrition, Health and Aging. Accepted.