Cover Page

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Cover illustration

Paul Powis, *Polish Chess Players in Kensington gardens*, London, during the 1970's, acrylic on card.

Powis used to take a walk through Kensington Gardens on Sunday afternoons. There is a large Polish community in Kensington. When Hitler invaded Poland at the start of the second World War a large number of Polish men came to England to join the war effort; they even had their own squadron in the RAF. Many stayed on and it was a tradition that some met up in Kensington Gardens and played chess and flew kites. It was interesting that they played chess throughout the year: even in the cold. Powis thought it fascinating that the park had joggers and footballers doing physical exercise out in the park and they were doing mental exercise. He loved the fact that they were wearing overcoats sitting in deckchairs.

The painting was well received and was exhibited in the "Best of British Illustration: IMAGES" exhibition that toured the country at galleries throughout England. However when the painting was exhibited in Brighton Art Gallery someone came into the Gallery and stole it. Nothing else was taken and it has never been recovered.

Strategies in preventive care for older people

YVONNE MARIJKE DREWES

geboren te Utrecht

in 1969

PROMOTIECOMMISSIE

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Chapter 1

General introduction

GENERAL INTRODUCTION

It is universally acknowledged that older people differ greatly from each other. For example, there is the healthy (sometimes wealthy) person, aged 75 years and over, who plays tennis or golf, still volunteers for activities with a social interest, frequently goes on holiday, and is still working on lifestyle improvements. On the other hand, there is the fragile widowed patient with decreased cognitive function, with only moderate self-care and health illiteracy. Is it justified to categorise these two types of older individuals into the same group for preventive strategies, even though their life expectancy, and levels of wellbeing and functioning are very different?

In current national prevention programs no difference is made between these types of individuals. For example, for breast cancer screening the woman's age is the stratifying criterion (i.e. 50-75 years). In a civil court case challenging the age criteria laid down in the permit for performing preventive breast cancer screening, the applicants argued that selection on the basis of age constituted a forbidden form of age discrimination by excluding women older than 75 years. The court of appeal concluded, however, that the medical reasons underlying this form of different treatment objectively justified using age as a selection criterion. The court concurred with the State that issued the permit, that for some women aged over 75 years preventive breast cancer screening might be beneficial, but that a collective approach for women older than 75 years would not be effective.[1] Therefore, when more health-specific criteria have been developed, it is possible that age will no longer be the most suitable selection criteria. This reasoning might also be applicable to other types of preventive care for older people. The work in this thesis investigates the possibilities to develop subgroup-specific preventive strategies for older people.

Demography of older people

Worldwide, the proportion of aged persons is growing faster than any other age group.[2] It is estimated that in the Netherlands by 2040, 26% of the population will be aged 65 years and older; of these, about one third will be aged over 80 years. Moreover, by 2060 it is expected that the proportion aged over 65 years will increase to 39%.[3]

The relative growth of the aged population is partly due to the 'baby boom' after World War II and to the increasing life expectancy. In the period 1950-2010 in the Netherlands, the life expectancy of men increased from 70.4 to 78.8 years and for women from 72.7 to 82.7 years.[4] However, the growing life expectancy does not necessarily imply an increasing number of years without chronic disease. On the contrary, life expectancy without chronic diseases has decreased in the Netherlands:[5] e.g. diseases like coronary heart

disease, depression, anxiety disorders, diabetes, stroke and arthritis are responsible for the greatest number of years lived with disability.[6]

In the context of these demographic developments healthy aging is a prominent theme in current international health policy.[7-10] The goal of healthy aging is not only a matter of maintaining good physical and mental health, but also of older people remaining independent and participating in social activities. It is of considerable importance for the coming years to develop strategies in health care for older people, which not only contribute to life expectancy but also to functioning in daily life and wellbeing. Nowadays, the number of people available to work is about four times the population of older persons. Due to changes in demography in the future, this ratio will change: it is estimated that in 2039 the number of people available to work will be only about two times the size of the older population.[11] Therefore, a shortage of personnel in health care can be foreseen. This shortage might be compensated by increasing the independence level of older people, thereby reducing the need for professionals in health and home care.

Preventive strategies in older people

Aims

Preventive care traditionally refers to measures taken to prevent disease, injury and death. In older persons, however, no breakthroughs in the prevention and treatment of diseases are expected in the short term. Therefore, according to the Health Council of the Netherlands, prevention in older people might also be used to contribute to the goal of healthy aging, i.e. the maintenance of independence and wellbeing by preventing or postponing disability and social isolation. This functional approach seems to be more promising and may also limit the need for care.[12] However, research on the effectiveness of preventive strategies to contribute to independence is lacking.

Strategies

Preventive strategies can be classified into four types of approach: universal, selective, indicated, and care-related prevention. Universal and selective prevention are based on a collective approach, whereas indicated and care-related prevention need an individualized approach (Figure 1).[13-15]

Universal prevention is desirable for the population (or subgroups) in general and should be applied to persons not motivated by current complaints or symptoms. This category comprises all those measures which can be advocated for the general public, aiming at health improvement and a decrease in risk of disease. *Selective prevention* is recommended for specific groups in the population with increased risk, and aims at improve-

ment of health of these specific risk groups. The third class of preventive measures, called *indicated prevention*, encompasses individuals who do not yet have a diagnosed disease but who do have complaints or mild symptoms. The aim of indicated prevention is to prevent the onset of disease or health damage. The fourth category of preventive care is *care-related prevention*, which aims at individuals with an established disease to reduce the burden of disease and to prevent complications, comorbidity and disability.

According to this classification, preventive programs can be organized collectively or individually. However, it is still unclear which approach is appropriate in preventive care for older people. Since 2008, the Dutch Public Health Act (*Wet publieke gezondheid*: WPG) stipulates that the local authorities (more precisely city councils) are responsible for the provision of health care to the elderly, including systematic monitoring of the health status of older people and the early detection and prevention of specific disorders like comorbidity.[16] According to the Act's explanation memorandum, the central government aims at prevention of comorbidity and prevention of health problems like decubitus, undernutrition, dehydration and intertrigo.[17] This section of the Act is placed directly after the provisions on youth health care and suggests that elderly health care can follow the same standardized, programmatic approach as youth health care.
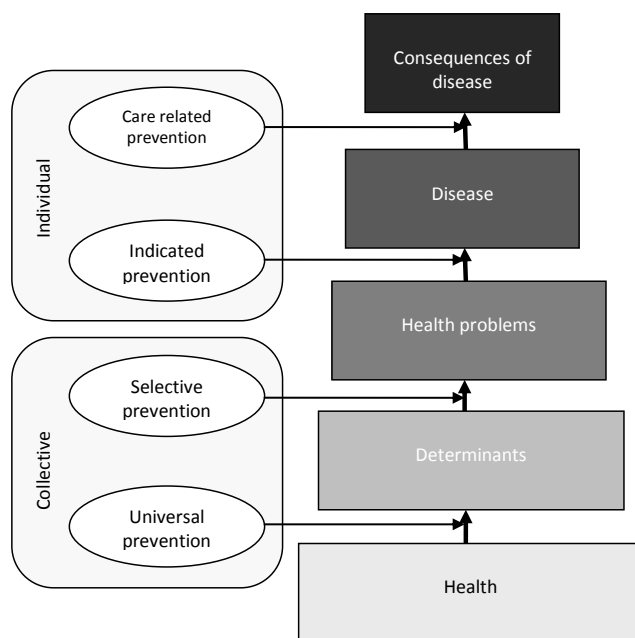

Figure 1. Classification of preventive strategies.[15]

However, it has been shown that a collective approach by screening community-dwelling older people for specific highly-prevalent disorders (such as hearing loss and impaired vision) is not effective.[18-23] Furthermore, screening older people for depressive symptoms by the general practitioner (GP) in order to offer them an intervention, was also not effective.[24] These screening programs did not fulfil the criteria for screening formulated in 1968 by Wilson and Jungner, in particular the criterion which demands that there should be an accepted treatment for patients with recognized disease and the criterion that the costs should be economically balanced in relation to possible expenditure on medical care as a whole.[25]

A possible explanation for the finding in these studies that a collective screening approach is not effective, is that in older persons health is a product of lifetime influences of diseases, lifestyle, environment and personal preferences in self-determination, accumulating in a variety of health status, functional status and expectations in older persons. Therefore, the perspectives on aged-related medical problems will differ considerably between older people. For example, is hearing impairment in older people a medical disorder or a normal, age-related decrease in functioning? A targeted approach to specific subgroups will probably be beneficial to prevent specific diseases or disorders, while a collective approach to the general older population is not effective.

Integration of subgroup-specific aims and strategies
Thus, for the development of effective preventive care for older people it is necessary to consider both the aim and the strategy. First, which aim of prevention should be pursued for older people: prevention of diseases and injury to contribute to life expectancy, or the maintenance of independence in daily life and wellbeing? Second, which strategy might be appropriate: a collective strategy targeting at (subgroups of) community-dwelling older people, or an individualized approach, targeting persons with complaints, symptoms or diseases for whom the preventive strategy can be customized to personal circumstances?

Figure 2 depicts these two dimensions of preventive care for older persons. This figure divides the preventive strategies into four quadrants, depending on the aim of prevention and the approach. In relation to this figure, the main question is: which preventive interventions for which subgroup of older persons might be applicable in each quadrant. To select these subgroups for interventions it is necessary to find predictors to stratify.
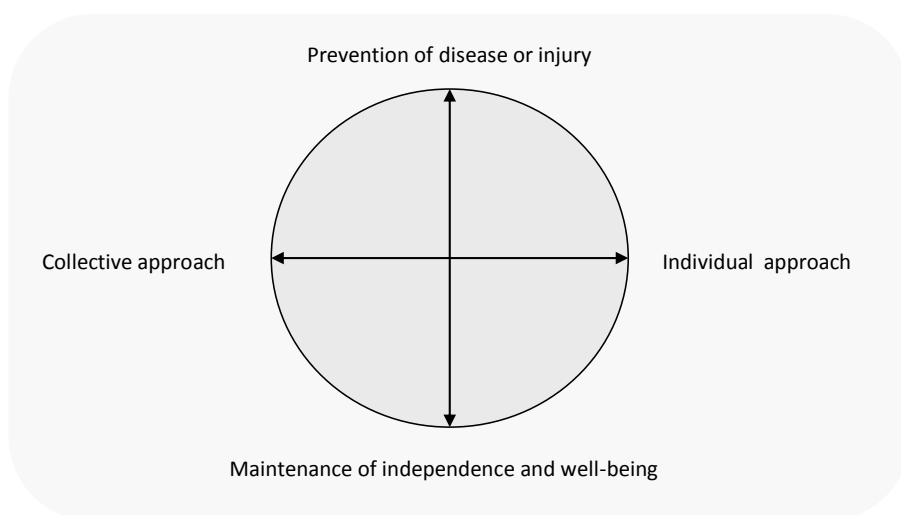
Figure 2. Aims and approaches in preventive strategies.

Current practice in the Netherlands

Activities to prevent disease

In current practice, the most prominent preventive activities for older people take place in order to prevent disease and therefore belong to the upper half of the circle. Below, two examples are described: the national programs for screening and for prevention, and cardiovascular risk management.

National programs for screening and vaccination

Breast cancer screening, colon cancer screening and influenza vaccination are collective preventive care strategies aiming to prevent disease, and fit in the left upper quadrant. These programs target subgroups of community-dwelling older people, defined by sex, age and specific indications, such as diabetes mellitus.

Cardiovascular risk management

Cardiovascular risk management, another prominent preventive activity in the Netherlands, also fits in the upper half of the circle. The aim of cardiovascular risk management is to reduce the incidence of cardiovascular events in a high-risk population. For prevention of cardiovascular disease both the collective and the individual approach is used. Prevention of cardiovascular disease in persons with a history of cardiovascular disease obviously follows an individual approach, because prevention of recurrent disease belongs to the care-related individual approach.

Providing lifestyle information to the general public by public health agencies and other organizations follows a collective approach. Another collective activity is the recently introduced 'prevention consultation' by GPs, which uses an open internet-based invitation to the general public to screen for risk factors for cardiovascular disease.[26] However, this consultation explicitly excludes older people because of their predetermined age-related higher risk.

Apart from these collective strategies, cardiovascular risk management for people without cardiovascular disease is mainly based on case finding carried out by GPs. Case finding comprises both selective prevention and indicated prevention. To identify individuals with a high cardiovascular risk, GPs often use clinical cardiovascular risk scores, such as the Framingham Risk Score[27] and the Systematic Coronary Risk Evaluation (SCORE).[28] However, their accuracy to predict risk on cardiovascular outcomes is clearly reduced in older persons.[29-32] Recently, the Leiden 85-plus Study and others have shown that homocysteine is predictive for cardiovascular events in old age.[33-38] However, it is not clear whether preventive cardiovascular treatment is more effective in a group of older people with high risk compared to older people with low risk.

Activities to maintain independence and wellbeing
In current practice, the market for general health checks is growing in the Netherlands. Especially so-called preventive health centers for seniors, to which older people are invited for a preventive check up, is an upcoming phenomenon. According to the policy document on this type of center, the aim of these centers is to improve social participation and social wellbeing, to enhance self-determination and to improve health literacy.[39] These centers use a collective approach, aiming at older people without using various selection criteria as are used for care-related or indicated prevention. Therefore, preventive health checks can be placed in the lower left quadrant. According to the preventive health center guidebook,[40] these centers try to reach this aim by screening older people for various conditions. However, evidence for the benefit of this type of screening is still lacking.[18-24]

Apart from these preventive health centers, a systematic approach to realize maintenance of independence and wellbeing (the lower half of the figure), is scarce. This does not mean that GPs and other caregivers do not work on the maintenance of independence and wellbeing in individual cases. However, apart from care-related prevention in the management of specific diseases, guidelines for maintenance of independence and wellbeing are lacking. To identify patients for whom preventive strategies aiming at maintenance of independence would be beneficial, instruments are needed to identify older people at high risk to develop disability in the near future. It is known that chronic

diseases[41-47] and multimorbidity[46-48] are strongly related with disability, but the predictive value of these factors for disability differs according to the health status of the older individual. When such instruments become available, older people can pro-actively be approached (collectively or individually) to prevent increase in disability, thereby resulting in the maintenance of independence and wellbeing.

Conclusion

In conclusion, in current practice, the most prominent preventive activities for older persons are related to the prevention of disease. However, there is room for improvement in the current cardiovascular risk management strategy, which is widely used for the prevention of cardiovascular disease in older persons. Moreover, it is still unknown which preventive activities can contribute to maintaining an acceptable level of functioning in daily life and wellbeing. In addition, instruments to identify eligible risk groups for this approach are lacking.

Therefore, it is important to explore the ideas of caregivers about the possibility to develop strategies in preventive care for older people to prevent disease or to maintain independence. To develop aim-specific collective preventive care for older persons, not only are instruments needed to define and select subgroups of older people at risk for disease or at risk for loss of independence, but also adequate interventions need to be available to prevent disease or to maintain independence.

Aim of this thesis

The general aim of the work in this thesis is to study the strategies in preventive care (varying in their aim and approach) for older people to facilitate the development of subgroup-specific evidence-based guidelines for preventive care for older persons.

To achieve this aim, the following questions were explored:

1. Is there scientific support for the idea that the aim of prevention is not only to prevent disease and injury, but also to maintain independence and wellbeing?
2. In order to aim at maintenance of independence and wellbeing:
a. Is it possible to identify older people who will benefit from a preventive approach which contributes to the maintenance of independence and wellbeing?
b. Which preventive strategies are appropriate to contribute to the maintenance of independence and wellbeing?
3. In order to aim at prevention of disease, with a focus on cardiovascular disease:
a. Is it possible to identify subgroups by screening older people to prevent disease?
b. Is a high-risk approach an appropriate preventive strategy to contribute to prevention of cardiovascular disease in older persons?

Brief description of chapters

1. Exploration of aims in preventive care for older people
Chapter 2 describes the perspectives of general practitioners (GPs) on preventive care for older people: these were examined in six focus groups. Perceptions of GPs regarding preventive care for older people, and the individual motivations of GPs for variation in preventive care, are largely unknown. Moreover, it is unclear whether GPs deliver preventive care in the traditional way, i.e. mainly to prevent diseases or injuries, or to maintain independence and wellbeing. Therefore, this qualitative study explores GPs' perspectives on preventive care to elucidate their ideas about the aim, organisation and content of preventive care for older people. This investigation will reveal the direction in which preventive care for older people, according to GPs, needs to be developed in the future.

2. Maintenance of independence and wellbeing
a. Specifying subgroups of older people
The aim of prevention probably depends on the health status of older persons, because values such as functioning in daily life and wellbeing become more important than life expectancy when the general health of older individuals declines.[12] To develop aim-specific evidence-based guidelines for preventive care for older people, instruments are needed to define and select subgroups. Chapter 3 describes the predictive value of multimorbidity for the development of disability in the general population of very old people and the role of cognitive impairment in this association. Chapter 4 investigates the variation in vulnerability concepts between the GPs and determines whether GPs have common or distinctive concepts of vulnerability in mind. If the variability between GPs proves to be small, assessment by GPs could be an effective instrument to select older people for geriatric care.

b. Preventive strategies to maintain independence and wellbeing
After exploring the possibilities to define subgroups, we investigated which conditions are appropriate for a collective approach to maintain independence and wellbeing. In Chapter 5 a RAND/UCLA appropriateness method was carried out to identify appropriate screening conditions to prevent functional decline in older people, stratified for age and vulnerability.

3. Prevention of disease with a focus on cardiovascular disease
a. Specifying subgroups of older people
In current guidelines for cardiovascular risk management, which primarily aim at preventing disease, the cardiovascular risk determinants (as selection criteria for preventive cardiovascular treatment) are insufficient for older persons. To select subgroups of older

people who are expected to derive the most benefit from preventive cardiovascular treatment, appropriate risk stratification instruments are needed. Furthermore, the influence of cardiovascular disease on the maintenance of independence and wellbeing needs to be investigated, because prevention of non-fatal cardiovascular disease probably not only improves life expectancy but also functional status and wellbeing. Chapter 6 investigates whether there are differences in prognosis between very old people with various levels of prevalent cardiovascular disease, compared to those with no manifest cardiovascular disease. The prognosis was studied not only with regard to incident cardiovascular morbidity and mortality, but also with respect to functional status. If risk stratification proves predictive not only for morbidity and mortality but also for functional status, then cardiovascular risk stratification will contribute to both aims, i.e. the prevention of disease and the maintenance of a person's independence.

b. Preventive strategies in cardiovascular risk management

Chapter 7 describes the effect of preventive pravastatin treatment in older people stratified into three groups at risk for cardiovascular disease based on their plasma levels of homocysteine. Since, according to Wilson and Jungner, risk predictors are clinically meaningful only when effective preventive treatment is available,[25] we need to establish which treatment possibilities are appropriate for older persons with high homocysteine to lower their cardiovascular risk. Therefore, a post-hoc subanalysis was performed in PROSPER[49] (a large double-blinded randomized placebo-controlled trial) to assess the effect of pravastatin on the risk for coronary heart disease and mortality in older persons, stratified for plasma levels of homocysteine.

General discussion and summary

Chapter 8 presents a general discussion on the main findings of the work in this thesis, considers the clinical implications of the results, and makes some recommendations for further research. Chapters 9 and 10 present a summary of this thesis in English and in Dutch, respectively.

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Chapter 2

GPs' perspectives on preventive care for older people: a focus group study

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ABSTRACT

Background
Preventive care traditionally aims to prevent diseases or injuries. For older people, different aims of prevention, such as maintenance of independence and wellbeing, are increasingly important.

Aim
To explore GPs' perspectives on preventive care for older people.

Design and setting
Qualitative study comprising six focus groups with GPs in the Netherlands.

Method
The focus-group discussions with 37 GPs were analysed using the framework analysis method.

Results
Whether or not to implement preventive care for older people depends on the patient's individual level of vitality, as perceived by the GP. For older people with a high level of vitality, GPs confine their role to standardised disease-oriented prevention on a patient's request; when the vitality levels in older people fall, the scope of preventive care shifts from prevention of disease to prevention of functional decline. For older, vulnerable people, GPs expect most benefit from a proactive, individualised approach, enabling them to live as independently as possible. Based on these perspectives, a conceptual model for preventive care was developed, which describes GPs' different perspectives toward older people who are vulnerable and those with high levels of vitality. It focuses on five main dimensions: aim of care (prevention of disease versus prevention of functional decline), concept of care (disease model versus functional model), initiator (older persons themselves versus GP), target groups (people with requests versus specified risk groups), and content of preventive care (mainly cardiovascular risk management versus functional decline).

Conclusion
GPs' perspectives on preventive care are determined by their perception of the level of vitality of their older patients. Preventive care for older people with high levels of vitality may consist of a standardised disease-oriented approach; those who are vulnerable will need an individualised approach to prevent functional decline.

HOW THIS FITS IN

Preventive care usually refers to measures that are taken to prevent diseases and injuries. In this study, GPs described the need for a paradigm shift in preventive care for older people. In persons with high levels of vitality, they found it important to focus on preventing or postponing diseases as in younger age groups, preferably with standardised programmes. However, in vulnerable older people this study found that preventive care needs a more individualised approach that takes the preferences of the older person into account and facilitates their most important needs.

INTRODUCTION

Preventive care traditionally refers to measures taken to prevent disease or injury and not to goals that are less well defined, such as maintenance of independence or wellbeing. However, for older people whose general health status is declining, values such as maintenance of independence in daily life and wellbeing become increasingly important.[1]

The possibility of preventive care contributing to independence and functioning in the daily life of older people is relatively new in current health policy.[2–4] Research on routine comprehensive screening for unmet health needs in the older population has revealed little or no benefits to the quality of life or health outcomes from such population screening;[5] despite this, the belief that screening could prevent functional impairment in older people has an enduring appeal to researchers, clinicians, and older people.[6,7]

In The Netherlands, preventive care for older people is generally delivered by the GP. Aside from national prevention programmes (for example, breast-cancer screening), preventive care is part of the regular primary care that is outlined in the Dutch College of General Practitioners' practice guidelines.[8] These guidelines are disease oriented and contain measures to prevent or cure diseases; they are not specifically aimed at less well-defined goals such as the maintenance of independence or wellbeing. GPs are allowed to deviate from the guidelines, depending on the needs of the individual patient. In The Netherlands, care delivered by GPs is accessible for everyone: it is part of the obligatory basic healthcare insurance and national prevention programmes are collectively financed.

Dutch GPs differ with regard to the type and intensity of preventive care delivered to their individual patients.[9,10] However, GPs' perceptions regarding preventive care for older people, and their individual underlying motivations for these variations, are largely unknown. Moreover, it is unclear whether GPs deliver preventive care in the traditional way — mainly to prevent diseases and injuries — or to maintain independence and wellbeing. This qualitative study explores GPs' perspectives on preventive care to elucidate their ideas about the aim, organisation, and content of such care for older people. The exploration of this facet of care delivery will show the direction in which preventive care for older people, according to GPs, needs to be developed in the future.

METHOD

In 2007, six focus-group discussions with GPs were conducted. To elicit GPs' own perspectives on preventive care for older people, this qualitative method was chosen to allow participants to articulate and discuss their own reasoning and strategies. Focus-group discussions were carried out instead of individual interviews as this method allows for interaction between the participating GPs; in-depth, emerging, complex concepts (for example, vitality) were explored and there was an opportunity for individuals to be probed for additional information.

Participants

Participants for the focus-group discussions were invited to attend via several channels. A general mailing list of GPs from the northern part of the South Holland province was used, with individuals being invited to attend by a letter that contained four dates. The GPs were divided into four groups (between four and eight GPs per group) according to their preferred date for the discussion. Besides this, to ensure the inclusion of GPs specialised in the care of older people and GPs with scientific expertise, a purposive sampling was undertaken: GPs with special interest from the postgraduate specialisation in elderly care who had already worked as a GP for many years were recruited (n=7). Moreover, to ensure inclusion of GPs with scientific expertise, GPs (n=6) from the Department of Public Health and Primary Care of Leiden University Medical Center were purposively sampled. To ensure that these specialist GPs would not dominate the discussions, they were separated from the other GPs and formed two extra focus groups.[11]

Interview guide and data collection

An interview guide to explore GPs' ideas about preventive care for older people was developed. The first questions asked participants to think broadly about their care for older people in general, their perceptions of aging, and the influence of geriatric care on primary care. Thereafter, the guide focused on the appropriateness of preventive health checks, as well as the aim, organisation, and content of preventive care for older people.

This interview guide was piloted in the first discussion group, after which only minor adjustments were made. As the guide remained largely the same, the data from the pilot group were included in the final analyses.[12]

Prior to the discussion, participants gave written consent and completed a brief questionnaire about their general practice and experience; they were assured that all comments would remain confidential. Each focus group was led by a researcher who was experienced in moderating such groups and assisted by another team member. Each

session lasted approximately 90 minutes (range 80–130 minutes). The researchers made field notes and debriefed after each session. Audiotapes were transcribed and promptly reviewed in order to clarify any unclear comments and/or to link each comment to the relevant participant.

Coding and analysis

Following the framework analysis method,[13,14] each transcript was read multiple times. Using thematic content analysis with an open coding system, themes emerged and were placed in an analytical framework for axial coding; this was discussed by the researchers until consensus was reached. Two researchers coded the data independently to increase reliability. New codes were added when considered necessary. Atlas.ti 5.2 was used for the analysis. After coding, the data were sorted according to the themes. The final stage of the analysis examined the relationships between the codes; this resulted in a conceptual model of GPs' perspectives of preventive care for older people.

RESULTS

Thirty-seven GPs — 22 males and 15 females — participated in the focus-group discussions. Of these, 27 (73%) had worked in general practice for ≥10 years. Twelve GPs (32%) reported working in practices with an over-representation of patients aged ≥65 years.

The major theme in the focus-group discussions was that GPs' approaches to preventive care for older people depended on the level of vitality of the individual person, as perceived by the GP.

Five subthemes were identified:
· aim of care;
· concept of care;
· initiator;
· target groups; and
· content of care.

The findings form the basis of this study's conceptual model for preventive care for older people (Figure 1), which comprises these five subthemes as dimensions. This model describes a shift in the perspective of GPs regarding older populations who have high levels of vitality or are vulnerable; when older people become more vulnerable, the scope of preventive care shifts within the five dimensions. Substantive differences in perspectives between the three types of GPs in the focus groups were not found,

although, as expected, the GPs with special interest were more used to discussing and reflecting on their perspectives about preventive care for older people.

Level of vitality

During the discussions, the focus of preventive care for older patients appeared to depend not on age, but on the level of vitality of the individual person as perceived
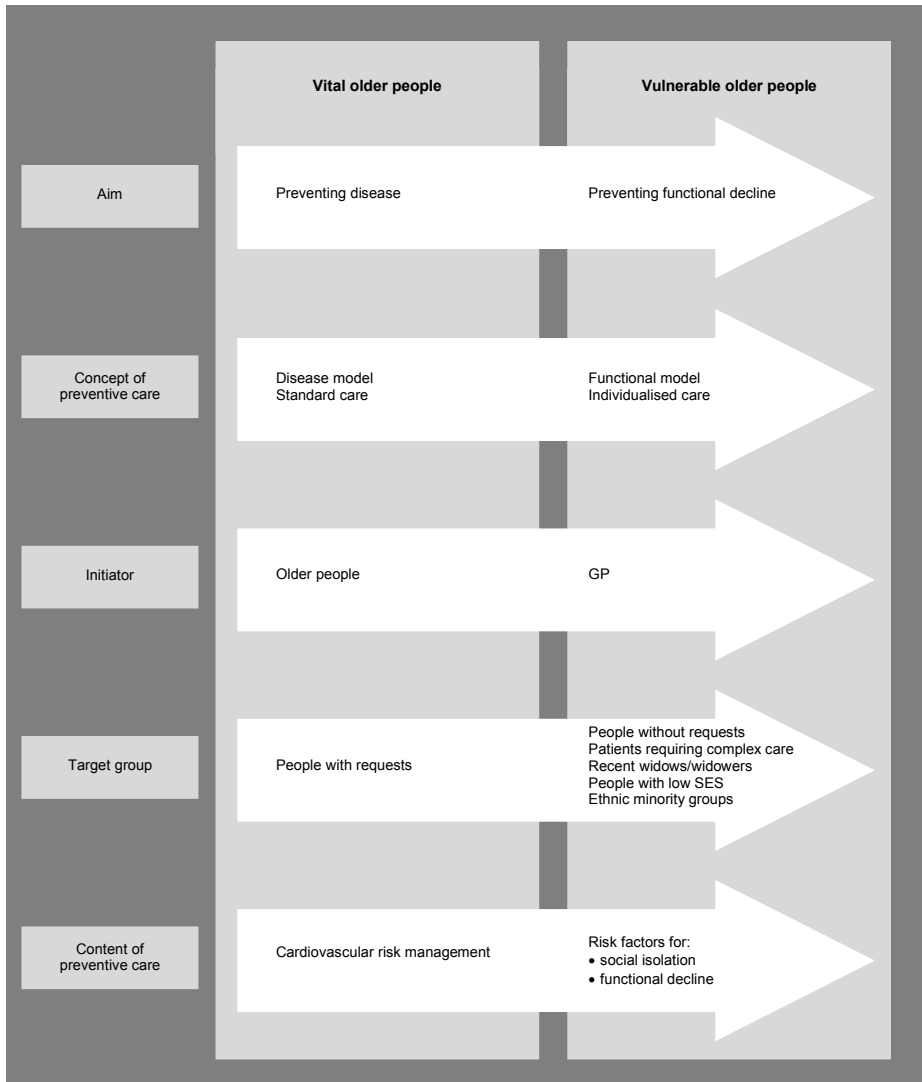

Figure 1. Conceptual model of preventative care for older people based on the present study, showing a shift in the perspective of GPs towards the vital and the vulnerable older populations.
SES = socioeconomic status

by the GP. GPs were primarily concerned about patients who they considered to be vulnerable and discussions mainly focused on the prevention of functional decline in this group. GPs differentiated between older people who are vulnerable and those with high vitality levels; biological age appeared to be more important than chronological age. Furthermore, GPs reported that their perception of old age also depended on their own age — the older they became, the higher were the age levels they used to classify someone as 'old'. In all discussions, the perceived level of vitality tended to influence the GP's policy:

'I don't like to focus on age limits. I've heard of the term "frailty" and think it's a good word to express vulnerability; I try to find out how vulnerable someone is and work within those limits.'
   (Female, focus group 3, general GP).

Although definitions of older people with high levels of vitality and those who were vulnerable were not specifically discussed, there was no confusion among the groups about these two 'types' of older people, especially when they talked about the extremes as examples. All GPs appeared to have an internalised concept of 'vitality' and 'vulnerability'.

Aim of prevention

In the population with high levels of vitality, GPs aimed at preventing or postponing disease, especially cardiovascular disease. For those who were more vulnerable, they attempted to contribute to the patient's quality of life by preventing or postponing functional decline, thereby enabling these patients to remain living independently at home for as long as possible:

'… when I start talking about prevention, the first thing that crosses my mind is the prevention of breast cancer, of cervical cancer, or the prevention of … something specific. At this stage of their life this type of thinking is useless … What I'd like to see regarding prevention for the elderly is to maintain their standard of living, and all the things that are important to them, for as long as possible.'
   (Male, focus group 2, general GP).

Concept of preventive care

To achieve the various goals of prevention, GPs described the need for a paradigm shift in practice. In persons with high levels of vitality, they found it important to focus on preventing or postponing diseases (as in younger age groups), preferably with standardised programmes, such as those available for breast-cancer screening for persons aged ≤75

years and cardiovascular health checks. In older people who are vulnerable, however, they found that preventive care needed a more individualised approach that took the preferences of the older person into account and facilitated their most important needs:

'I should be helping people cope better with their simple daily tasks, like being able to write and cut up their own food — it's a different way of thinking. It's looking at their situation from another angle. At this stage I have to forget the idea that I'm the "curing doctor" who only acts in response to their complaints …'
    (Male, focus group 3, general GP).

This change in attitude and focus of care for older people who are vulnerable was clearly described by a GP who specialised in geriatric care:

'In the last few years, an important learning point for me has been to get away from the "disease" model and move over to the "functional" model.'
    (Female, focus group 6, GP with special interest).

Initiator for prevention

In general, GPs tended to hesitate about giving preventive advice to older people. They doubted the usefulness of such advice, as the person had already reached a respectable age without it:

'The older you are, the more you have proven your point'.
    (Female, focus group 5, general GP).

This was particularly considered to be the case for those with a good quality of life; GPs preferred to play 'a waiting game' because they were afraid of 'patronising' their patients:

'I'd always like to have some excuse to get a process going. I do agree with prevention … but there'll always be that association with the idea of "patronising" people and worrying about medicalisation.'
    (Female, focus group 1, GP with special interest).

One GP, whose patients participated in a study on the prevalence and incidence of risk factors for chronic diseases in older people, noted that some individuals could be motivated to change their lifestyle when, for example, abnormal laboratory tests were found. Usually, however, GPs assumed that people without a perceived need for help were not sufficiently motivated to adhere to preventive advice, especially that relating to lifestyle.

Some GPs described a more proactive role in their preventive care for the older people they considered to be more vulnerable. GPs wanted to become acquainted with this population and to try to anticipate crises. They were also aware that some older people had lost their autonomy and had become increasingly dependent on them; some felt a considerable amount of responsibility for this kind of patient:

'Once people are over the age of 90, you get the idea that you're probably the most important person in their life.'
    (Male, focus group 1, GP with special interest).

GPs behaved proactively by making home visits, and by developing a proactive attitude in their consultations:

'I mainly think of the extra task that one gets as "care manager" … that you're the initiator of a "care process" in which you try to do as little as possible, but you have to initiate it to make sure that the elderly are able to live their lives as comfortably as possible.'
    (Male, focus group 1, GP with special interest).

Whereas some GPs did not make home visits (doubting its usefulness), most saw the benefit of these; such visits were seen as a way to monitor the home situation, such as checking the refrigerator or controlling medication use:

'I think it's a good thing that, once in a while, you visit people who live on their own … it's partly just to keep an eye on them.'
    (Male, focus group 1, GP with special interest).

Target groups

For older people with high levels of vitality, GPs mainly targeted those who actively asked for preventive care. Apart from the national prevention programmes (for example, breast cancer screening and the influenza vaccination) and regular cardiovascular risk management, GPs tended to limit prevention for this population to 'prevention on request'. Some GPs said they were most worried about older people who did not consult them, especially those who were isolated and vulnerable. They actively approached this group to prevent crisis situations:

'I worry more about the people who don't come to see me than about those who do. Then I go along to see them and say: "I haven't seen you for a while. Are you OK?"'
    (Male, focus group 2, general GP).

The GPs also considered older people who were single or recently widowed to be vulnerable. Some noted mortality dates in their agenda and visited widows/widowers on appropriate days. Single older people were considered susceptible for social isolation:

'… but the most important criterion is whether or not they live alone. We tend to keep a special eye on these people.'
   (Male, focus group 3, general GP).

Other target groups were those with a low socioeconomic status and ethnic minority groups: these lacked health education more often and belonged to the vulnerable group because they were at high risk of developing health problems. This could be a result of it being difficult to give lifestyle advice due to language problems:

'Another group are the elderly immigrants with communication problems. So one is already satisfied if you're just able to arrange basic care for them, but once you start to explain what they could change to make things better for themselves, that's when the misunderstandings start. That makes things really difficult, so then you settle for less.'
   (Male, focus group 1, GP with special interest).

Alternatively, when some individuals become more vulnerable, their already disadvantaged social position worsens, leading to more problems such as isolation and multimorbidity:

'When I look at my own patients I see very many "lost" elderly persons … they already have a disadvantaged position, and the older they get, the greater the disadvantage becomes … more isolation and, of course, much more morbidity and comorbidity.'
   (Male, focus group 6, GP with special interest).

Content of preventive care
For both groups of patients – those with high levels of vitality and those who were vulnerable – physical activity was frequently mentioned as an important way to maintain or improve their state of health and functioning:

'Well, keeping mobile plays a major role in staying healthy. If you just sit and stop moving and if you're overweight, then you'll never start moving again.'
   (Male, focus group 1, GP with special interest).

Furthermore, according to the GPs, the content of preventive care should differ between both groups. In those with high levels of vitality, cardiovascular risk management was considered the most important topic:

'For the active 60-plussers, I can imagine that stroke prevention is a much more important item for them.'
  (Male, focus group 6, GP with special interest).

Some GPs carried out a cardiovascular health check on request and a few routinely offered such checks to all older persons above, for example, the age of 60 years.

In the population that was considered to be vulnerable, preventive care was mainly aimed at quality of life. Prevention of social isolation and functional decline was considered important, with hearing/visual impairment, cognition, depressive symptoms, mobility, prevention of falls, and nutrition being the main topics:

'Concerning prevention, I think we have to closely monitor how well the elderly are able see and hear … if that ability starts to deteriorate I'd like to check it … just to make sure that they can still do the few things that make life enjoyable for them … like being able to write and read.'
  (Male, focus group 2, general GP).

DISCUSSION

Summary
According to the GPs in this study, the need for preventive care depended on the level of patients' vitality, as perceived by the GP. As such, the focus of preventive care should differ between older people with high levels of vitality and those who are vulnerable. A conceptual model of preventive care for older people was constructed, showing the difference in GPs' perspectives towards these groups. According to this model, preventive care comprises five dimensions (aim of care, concept of care, initiator, target groups, and content of care); when older people become more vulnerable, the scope of preventive care shifts within these five dimensions.

In general, GPs appeared to be more focused on preventive care for people who were vulnerable than for those with high levels of vitality. They expected most benefits of preventive care to be gained by allowing those who were vulnerable to live as independently as possible and by preventing their functional decline. For the population with

high levels of vitality, the GPs restricted their role to the traditional one of preventing diseases and injuries, for example, by applying cardiovascular risk management. GPs assumed that people without a perceived need for help were not sufficiently motivated to adhere to preventive advice; their doubt about the value of their advice suggests that GPs are making judgments about people's risks and their ability to change, which might not be appropriate.

Strengths and limitations

Focus group discussions were considered to be the preferred way to explore the perceptions of GPs regarding preventive care for older people. With a systematic approach, an analytical framework was developed that was discussed by the researchers until consensus was reached. To the authors' knowledge, this is the first study to examine the attitudes of GPs towards preventive care for older people.

A possible limitation of this study is that clear definitions of older people who were vulnerable, or had high levels of vitality, were not specified; however, during the discussions there was no confusion about these two categories of older people. In general, GPs have an internalised concept of 'vitality' and 'vulnerability; those who are vulnerable are characterised by increased prevalence of diseases and disorders, a poorer prognosis, disability of various kinds, and multiple simultaneous problems.[15,16] Furthermore, the level of vitality is a continuous scale and the perspectives of the GPs seemed to vary along this. The majority of people will be somewhere between these two extremes.

Other potential weaknesses are that only one national health system was investigated, and health professionals in no discipline, other than general practice, were interviewed. Furthermore, the GPs volunteered to participate and only their opinions, not their daily practices, were investigated.

Comparison with existing literature

Much research has shown that for older people living in the community, a systematic screening approach is not effective for highly prevalent disorders.[7,17–22] The current study confirms this finding: GPs stated that preventing or postponing disability in people who are vulnerable needs an individualised approach rather than a systematic screening approach. However, according to Nielen et al, GPs have a positive attitude towards primary prevention of cardiovascular diseases if detection focuses on the group of patients at risk.[23] The discussions in the focus groups also show that a standardised approach for topics such as cardiovascular risk management can be useful for people who have high levels of vitality, with the aim of preventing diseases by early detection of them or appropriate risk factors.

How to identify and classify older people into those who are vulnerable and those who have high levels of vitality were not discussed in the focus groups. As GPs want to apply different preventive care to these groups, the current study suggests that it is important for preventive care to develop a tool to identify these groups of older people.[24,25]

Phelan et al described that older persons from an ethnic minority and those with a low socioeconomic status are at higher risk for diseases and disorders, and do not derive equal benefit from the current capacity to control disease and death.[26] GPs in this study were aware of these higher risks and the need for a more individualised proactive approach, but described difficulties in implementing this. It would seem that more effort needs to be put into preventive care for these groups, even when the approach for older people who are vulnerable is applied to them.

Implications for practice and research

This study's findings are based on GPs' reported behaviour; the extent to which this mirrors actual behaviour remains a topic for further empirical research. In addition, more research is needed into the way that GPs assess the vitality of older people in practice and the effects of those assessments on their actual behaviour and the care outcomes.

This study highlights the need for more research on the ways in which preventive care for older people who are vulnerable and those who have high levels of vitality can be improved, focusing on ethnic minorities and people with a low socioeconomic status. This relies on being able to define those who are vulnerable and those with high vitality levels; this distinction needs to be clarified in future research.

To verify this study's findings, other studies need to be undertaken in order to explore how the model fits in with the perspectives of other GPs and in other countries. In addition, the perspective of older patients should be addressed. Insight into both viewpoints will help negotiate care goals that result in shared decision making that truly is shared between the GP and the patient.

In the opinion of GPs, preventive care for older people who have high levels of vitality can follow a standardised approach; such care for people who are vulnerable, however, needs an individualised approach to prevent functional decline and to allow them to live as independently as possible for as long as possible.

ACKNOWLEDGMENTS

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Chapter 3

The effect of cognitive impairment on the predictive value of multimorbidity for the increase in disability in the oldest old: the Leiden 85-plus Study

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ABSTRACT

Background

Prevention of disability is an important aim of healthcare for older persons. Selection of persons at risk is a first crucial step in this process.

Objectives

This study investigates the predictive value of multimorbidity for the development of disability in the general population of very old people and the role of cognitive impairment in this association.

Design

The Leiden 85-plus Study (1997–2004) is an observational prospective cohort study with 5 years of follow-up.

Setting

General population of the city of Leiden, The Netherlands.

Subjects

Population based sample of 594 participants aged 85 years.

Methods

Disability in activities of daily living (ADL) was measured annually for 5 years with the Groningen Activity Restriction Scale (range 9–36, 9=optimal). Multimorbidity is defined as the presence of two or more chronic diseases at age 85 years. Cognitive function was measured at baseline with the mini-mental state examination (MMSE).

Results

At baseline participants with multimorbidity had higher ADL disability scores compared with those without [median 11 inter-quartile range (IQR 9–16) versus 9 (IQR 9–13) ADL points, Mann–Whitney U test p <0.001]. Stratified into four MMSE groups, ADL disability increased over time in all groups, even in participants without multimorbidity (p trend <0.001). Multimorbidity predicted accelerated increase in ADL disability in participants with MMSE of 28–30 points (n=205, 0.67 points/year, p <0.001), but not in participants with lower MMSE scores (all p >0.100).

Conclusion

The predictive value of multimorbidity for the increase in ADL disability varies with cognitive function in very old people. In very old people with good cognitive function,

multimorbidity predicts accelerated increase in ADL disability. This relation is absent in very old people with cognitive impairment.

KEY POINTS

·   The predictive value of multimorbidity for the increase in disability in ADL varies with cognitive function.
·   Multimorbidity does not predict accelerated increase in disability in ADL in older persons with cognitive impairment.
·   Only in older persons with good cognitive function, multimorbidity predicts accelerated increase in disability in ADL.
·   For selection of high-risk patients, multimorbidity can be used only in those older persons without cognitive impairment.

INTRODUCTION

The aim of preventive programmes for older people is to enable them to live as independently as possible for as long as possible. For these programmes instruments are needed to identify older people at high risk to develop disability in the near future. When such instruments are available, older people can pro-actively be approached to prevent increase in disability.

It is known that chronic diseases[1-7] and multimorbidity[6-8] are strongly related with disability. However, most of these studies incorporated cognitive impairment or dementia in their multimorbidity scores. Because earlier studies showed strong associations between cognitive function and disability,[2-4,6-13] the predictive value of multimorbidity for disability may differ between persons with and without cognitive impairment.

Therefore, we studied the predictive value of multimorbidity for the increase in disability in activities of daily living (ADL) in older persons with and without cognitive impairment.

METHODS

Setting and study population

The Leiden 85-plus Study is an observational population based prospective follow-up study of 85-year-old inhabitants of Leiden (The Netherlands). Between September 1997 and September 1999, all inhabitants of Leiden who reached the age of 85 years were invited to participate in the study.

Participants were followed for 5 years until the age of 90 years or until death. Date of death was obtained from the municipality. All participants were visited annually at their place of residence where face-to-face interviews were conducted, cognitive testing was performed, and disabilities in basic ADL were measured.

All participants gave their informed consent; for those with severe cognitive impairment, informed consent was obtained from a proxy. The Medical Ethics Committee of Leiden University Medical Centre approved the study. For the present study, participants with missing ADL measurements at baseline and participants with missing information on the presence of two or more chronic diseases at baseline were excluded.

Main study parameters

Determinants

Information on the presence of chronic diseases at baseline was obtained from the participant's general practitioner (GP), nursing home physician and/or pharmacy records. We included common chronic diseases in the analyses, which are commonly used in multimorbidity scores:[14,15] arthritis, chronic obstructive pulmonary disease (COPD), diabetes mellitus, heart failure, stroke, Parkinson disease, depressive symptoms reported in the previous year, and history of cancer or myocardial infarction. COPD was considered present when lung medication [Anatomical Therapeutic Chemical (ATC) code R03] was used at age 85 years. Multimorbidity was defined as the presence of two or more of the nine chronic diseases investigated.

Cognitive function was assessed with the mini-mental state examination (MMSE), with scores ranging from 0 to 30 (=optimal function)[16] and was stratified in four groups: MMSE score <19 points (severe cognitive impairment), 19–23 points (moderate cognitive impairment), 24–27 points (mild cognitive impairment) and 28–30 points (optimal cognitive function).

Outcome

Disability in basic ADL was determined with the Groningen Activity Restriction Scale, which assesses an individual's competence in the following nine basic activities: walk inside, get up out of bed, get into and out of a chair, visit the toilet, wash hands and face, wash body, dress and undress, eat and drink and make breakfast.[17,18] Questions are phrased: "*Can you, fully independently,…?*". Answers range from "*Fully independently, without any difficulty*" (1 point) to "*Not fully independently, only with someone's help*" (4 points). The total ADL disability score ranges from 9 to 36.

Data analysis

In the cross-sectional analysis, median scores of ADL disability at age 85 years between participants were compared using the Mann–Whitney U test.

Prospectively, the relation between individual chronic diseases and multimorbidity at baseline and changes in ADL-disability scores over time were analysed with linear mixed models. Each linear mixed model included the individual disease a term for time, and a term for the interaction between disease and time. The results of the linear mixed models are as follows: the effect of time on disability in ADL reflects the annual change in ADL disability in those without the disease, and is presented as basic annual change in ADL disability score. The interaction of an individual chronic disease and time reflects the

additional annual change in ADL disability for those with the disease and is presented as additional annual change in ADL disability score.

To assess the influence of cognitive impairment, participants were stratified into four groups according to their baseline MMSE score (0–18, 19–23, 24–27 and 28–30)[19] and the predictive effect of multimorbidity on changes in disability in ADL were examined separately in these four groups.

Data were analysed using SPSS 16.0 (Chicago, IL, USA).

RESULTS

Study population
Between September 1997 and September 1999, 705 inhabitants of Leiden reached the age of 85 years and were eligible for participation in the study. A total of 14 persons died before enrolment in the study, 92 declined to participate, no ADL measures were available for two persons, and for three persons information on the presence of two or more chronic diseases was missing. Therefore baseline data were available for 594 participants. Appendix 1 shows the numbers of participants at the start of the study and annually over the 5-year follow-up period.

Cross-sectional analysis
Table 1 presents the baseline characteristics, the prevalence of the investigated chronic diseases, and the prevalence of multimorbidity among the participants at age 85 years. In total, 34% of the participants were male. The prevalence of multimorbidity was 39%. Arthritis was the most common chronic disease (33%).

At baseline, participants with arthritis, depressive symptoms, diabetes mellitus, stroke and Parkinson disease had higher scores of ADL disability than participants without these diseases (Appendix 2). The greatest differences in median ADL disability scores between participants with and without an individual chronic disease were seen for Parkinson disease (19 versus 10 points, p <0.001) and stroke (15 versus 10 points, p <0.001). Participants with multimorbidity had higher ADL disability scores compared with those without multimorbidity (11 versus 9 points, p <0.001).

At baseline, highest ADL disability scores were found in participants with an MMSE score <19 (Figure 1). In the groups with MMSE scores of 19–23, 24–27 and 28–30, higher baseline ADL disability scores were found for participants with multimorbidity than for

Table 1. Baseline characteristics of the study population at age 85 years (n=594ᵃ).

	n	%
Sociodemographic characteristics		
Sex, male	201	34
Low level of education – primary school only	383	65
Prevalence of individual chronic diseases		
Arthritis	193	33
Depressive symptoms	125	21
History of cancer	104	18
Diabetes mellitus	86	15
Heart failure	75	13
COPD	70	12
Myocardial infarction	63	11
Stroke	61	10
Parkinson disease	15	2.5
Total number of chronic diseases		
None	147	25
One	213	36
Two or more (multimorbidity)	234	39
Classification in the mini-mental state examination (MMSE)		
MMSE <19 pts	97	16
MMSE 19-23 pts	85	14
MMSE 24-27 pts	207	35
MMSE 28-30	205	35

ᵃmissing data in n=0 to n=11 per disease; of 568 participants the data on chronic diseases were complete.
COPD = chronic obstructive pulmonary disease

participants without multimorbidity (all p ≤0.010). However, in subjects with an MMSE score <19, no differences in ADL disability scores were found between participants with multimorbidity and those without multimorbidity (median ADL disability scores: 19 versus 19 points, p=0.950).

Prospective analyses

Appendix 3 presents the relation of individual chronic diseases and multimorbidity with additional annual changes in ADL performance. In participants without any of the investigated chronic diseases, the basic annual change in ADL disability score was 1.2 points per year (95% CI 1.0–1.4, p <0.001, data not shown). Depressive symptoms, heart failure, myocardial infarction and stroke predicted an additional annual change in ADL disability score during follow-up. Other individual chronic diseases did not predict an additional annual change in ADL disability score (all p >0.100). Participants with mul-

timorbidity had an accelerated progression of ADL disability over time compared with those without multimorbidity: additional annual change 0.42 points (95% CI 0.21–0.63, p <0.001).

The effect of cognitive function on the predictive value of multimorbidity for disability in ADL was investigated by stratifying the participants into four groups according to their MMSE scores at baseline (Figure 2; Appendix 4). In all MMSE groups, ADL disability increased over time, independent of the presence of multimorbidity (basic annual change, p for trend <0.001).

Multimorbidity was associated with an additional annual change in ADL disability of 0.67 points (95% CI 0.39–0.95, p <0.001) in subjects with an MMSE score of 28–30. In participants with an MMSE score <28, multimorbidity did not predict the change in ADL disability (additional annual change, p for trend <0.001).
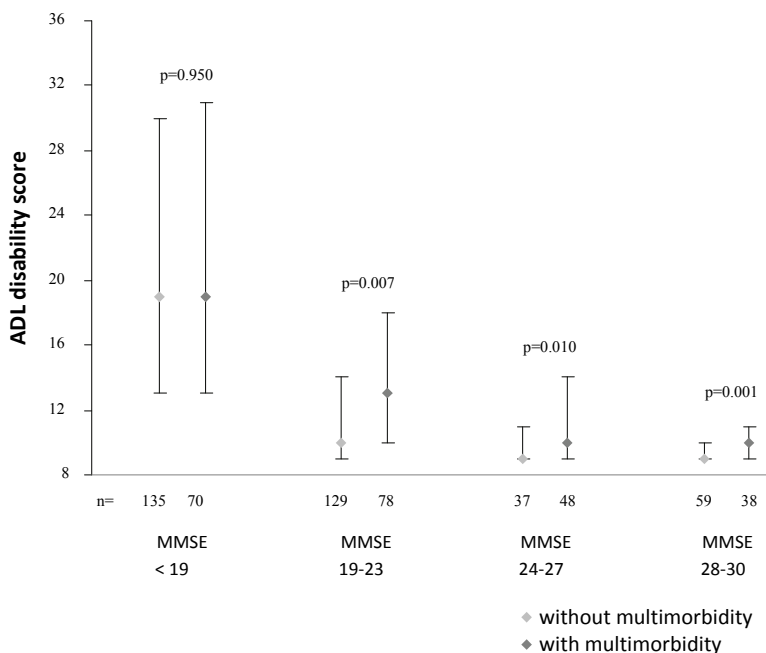

Figure 1. ADL disability scores dependent on the presence of multimorbidity at age 85 years stratified for cognitive function.
Data were presented as medians and corresponding inter-quartile ranges, p-values estimated with the Mann-Whitney U test; ADL, activities of daily living; MMSE, mini-mental state examination.
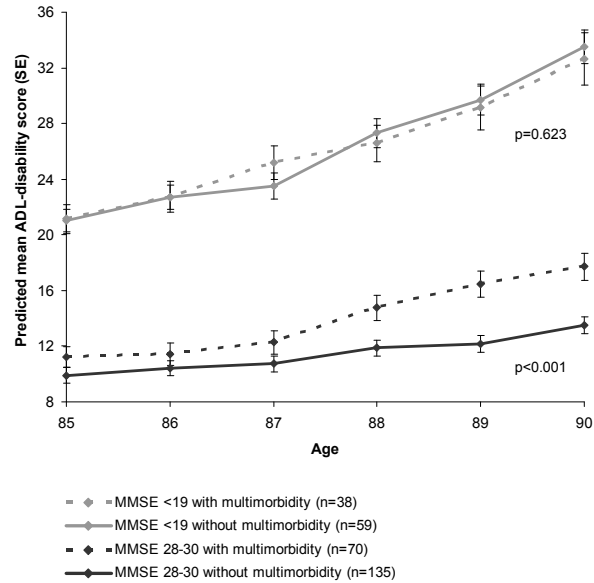
Figure 2. Changes in ADL-disability points over time depending on multimorbidity in participants from age 85 years onwards, for strata of cognitive function.
ADL, activities of daily living; MMSE, mini-mental state examination.

COMMENT

Principal findings

This population-based study of very old people demonstrates that disability in ADL increases over time in older persons of the general population. Multimorbidity only predicted accelerated increase in disability in ADL in older people with an optimal cognitive function (MMSE score ≥28 points). In persons with lower MMSE scores, this relation was not observed.

Our findings are in agreement with earlier studies showing that both cognitive impairment and multimorbidity are associated with the development of disability in ADL in older persons.[9-11,13,15,20] However, these studies did not report that this relation is only present in older people with MMSE scores ≥28 points. A possible explanation for these findings is that the effect of cognitive impairment on ADL performance overwhelms the effect of multimorbidity. Another possible explanation is the possibility that cognitive performance at the age of 85 years is a marker for the total health condition, with a high sensitivity to detect detrimental effects on ADL disability. In persons with cognitive impairment, we found large basic annual changes in ADL disability score, indicating that in persons with cognitive impairment ADL disability increases, independent of the presence of multimorbidity.

Strength and limitations

Our study has several strengths. The population-based setting and almost complete follow-up of the participants allow to generalise the conclusions to older people (aged 85 years and over) in the general population. It is important to study the development of disability in ADL in old age, because the very old are the fastest growing segment of the general population[21] and the prevalence of disability in ADL increases with age.[12,22,23] Therefore, disability in ADL in old age can have a significant effect on quality-of-life, healthcare needs and costs in our ageing society. Furthermore, the study stratified on cognitive function, allowing to investigate the predictive value of multimorbidity for disability in ADL at different levels of cognitive function.

A possible limitation of the present study is that we used a selection of only nine diseases, as diagnosed by physicians. The prevalence of multimorbidity might have been different when other chronic diseases had been included, or when more specific diagnostic tests had been used. In addition, we did not take the severity of the chronic diseases into account. However, our approach of multimorbidity, by using only data of the GPs, nursing home physicians and pharmacy records, reflects clinical practice and similar systems of adding individual diseases have been applied in many other studies.[8]

Clinical implications and future research

The most important clinical implication is that multimorbidity can only be used as a predictor for disability in ADL in older people with optimal cognitive function. Older people with an MMSE score less than 28 are at the highest risk for disability in ADL. However, multimorbidity is no longer an additional predictor of disability in ADL in this group. Preventive programmes to promote older people to live as independently as possible may use a two-stage screening test, which contains MMSE screening as a first step and multimorbidity screening as the second, to select older people at risk for disability.

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Appendices

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┌─────────────────────────┐
│        Eligible         │
│         n=705           │
└─────────────────────────┘
             │                    ┌──────────────────────────────────┐
             ├────────────────────│ Died n=14                        │
             │                    │ Refused n=92                     │
┌─────────────────────────┐       └──────────────────────────────────┘
│    Informed consent     │
│         n=599           │
└─────────────────────────┘
             │                    ┌──────────────────────────────────┐
             ├────────────────────│ Missing ADL measures n=2         │
             │                    │ Missing data >1 chronic disease n=3│
┌─────────────────────────┐       └──────────────────────────────────┘
│  Study population age 85│
│         n=594           │
└─────────────────────────┘
             │                    ┌──────────────────────────────────┐
             ├────────────────────│ Died n=45                        │
             │                    │ Refused n=37                     │
┌─────────────────────────┐       └──────────────────────────────────┘
│        Age 86           │
│        n=512*           │
└─────────────────────────┘
             │                    ┌──────────────────────────────────┐
             ├────────────────────│ Died n=54                        │
             │                    │ Refused n=13                     │
┌─────────────────────────┐       └──────────────────────────────────┘
│        Age 87           │
│        n=445            │
└─────────────────────────┘
             │                    ┌──────────────────────────────────┐
             ├────────────────────│ Died n=47                        │
             │                    │ Refused n=7                      │
┌─────────────────────────┐       └──────────────────────────────────┘
│        Age 88           │
│        n=391            │
└─────────────────────────┘
             │                    ┌──────────────────────────────────┐
             ├────────────────────│ Died n=51                        │
             │                    │ Refused n=9                      │
┌─────────────────────────┐       └──────────────────────────────────┘
│        Age 89           │
│        n=331            │
└─────────────────────────┘
             │                    ┌──────────────────────────────────┐
             ├────────────────────│ Died n=46                        │
             │                    │ Refused n=8                      │
┌─────────────────────────┐       └──────────────────────────────────┘
│        Age 90           │
│        n=277            │
└─────────────────────────┘
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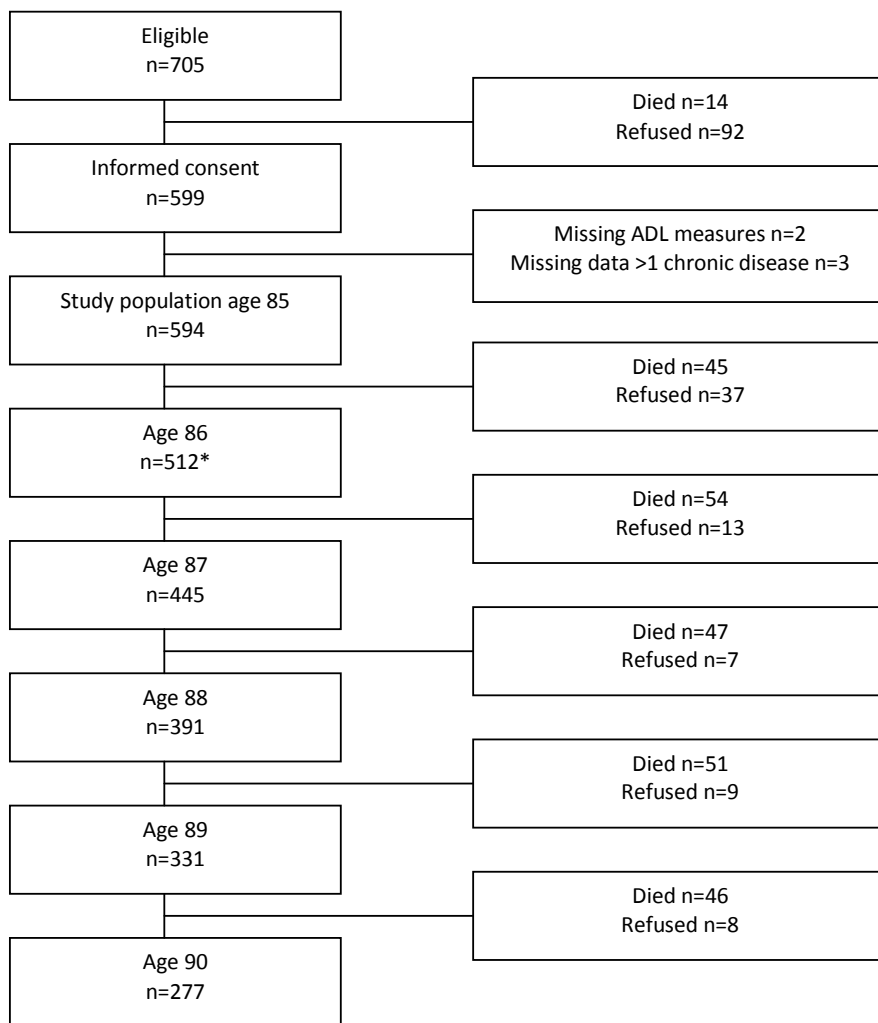
Appendix 1. Number of participants in the Leiden 85-plus Study at age 85 years (baseline) and annual follow-up measurements

*missing ADL measures at age 86 years: n=3

Appendix 2. Presence of chronic disease and ADL disability in participants aged 85 years (n=594).

| | Diagnosis | | | | |
| | Yes | | No | | |
	n	ADL disability	n	ADL disability	p-value
Individual chronic diseases					
Arthritis	193	11 (9-15)	399	10 (9-15)	0.024
Depressive symptoms	125	10 (9-16)	458	9 (10-14)	0.013
History of cancer	104	9 (9-13)	487	10 (9-15)	0.100
Diabetes mellitus	86	11 (9-17)	504	10 (9-14)	0.001
Heart failure	75	10 (9-17)	517	10 (9-14)	0.092
COPD	70	10 (9-14)	524	10 (9-15)	0.683
Myocardial infarction	63	10 (9-15)	529	10 (9-15)	0.779
Stroke	61	15 (10-29)	531	10 (9-13)	<0.001
Parkinson disease	15	19 (10-33)	579	10 (9-14)	<0.001
Multimorbidity	234	11 (9-16)	360	9 (9-13)	<0.001

Data presented as medians and corresponding interquartile ranges, p-values estimated with the Mann-Whitney U test; ADL = activities of daily living, COPD = chronic obstructive pulmonary disease

Appendix 3. Additional annual change in ADL disability depending on chronic diseases in participants from age 85 years onwards.

	Estimated points ADL disability (SE)	p-value
Individual chronic diseases		
Arthritis	-0.17 (1.1)	0.103
Depressive symptoms	0.42 (0.13)	0.001
History of cancer	-0.14 (0.15)	0.330
Diabetes mellitus	0.08 (0.16)	0.611
Heart failure	0.69 (0.18)	<0.001
COPD	0.12 (0.18)	0.489
Myocardial infarction	0.42 (0.19)	0.028
Stroke	0.95 (0.19)	<0.001
Parkinson disease	-0.37 (0.38)	0.333
Multimorbidity	0.42 (0.11)	<0.001

Estimated by linear mixed models; ADL = activities of daily living, COPD = chronic obstructive pulmonary disease

Appendix 4. Annual changes in ADL disability points depending on multimorbidity in participants from age 85 years onwards, stratified for cognitive function.

	Basic annual change		Additional annual change for pts with multimorbidity	
	Estimated points ADL disability	p-value	Estimated points ADL disability	p-value
MMSE < 19	2.4	<0.001	-0.21	0.623
MMSE 19-23	1.9	<0.001	-0.18	0.597
MMSE 24-27	1.2	<0.001	0.26	0.101
MMSE 28-30	0.68	<0.001	0.67	<0.001

Estimated by linear mixed models

ADL = activities of daily living, MMSE = Mini-Mental State Examination

Chapter 4

Variability in vulnerability assessment of older people by individual general practitioners: a cross-sectional study

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ABSTRACT

Background

In clinical practice, general practitioners (GPs) appeared to have an internalized concept of 'vulnerability'. This study investigates the variability between GPs in their vulnerability-assessment of older persons.

Methods

Seventy-seven GPs categorized their 75-plus patients (n=11392) into not vulnerable, possibly vulnerable and vulnerable patients. GPs personal and practice characteristics were collected. From a sample of 2828 patients the following domains were recorded: sociodemographic, functional [instrumental activities in daily living (IADL), basic activities in daily living (BADL)], somatic (number of diseases, polypharmacy), psychological (Mini-Mental State Examination, 15-item Geriatric Depression Scale; GDS-15) and social (De Jong-Gierveld Loneliness Scale; DJG) . Variability in GPs' assessment of vulnerability was tested with mixed effects logistic regression. P-values for variability (p_{var}) were calculated by the log-likelihood ratio test.

Results

Participating GPs assessed the vulnerability of 10361 patients. The median percentage of vulnerable patients was 32.0% (IQR 19.5 to 40.1%). From the somatic and psychological domains, GPs uniformly took into account the patient characteristics 'total number of diseases' (OR 1.7, 90% range=0, p_{var}=1), 'polypharmacy' (OR 2.3, 90% range=0, p_{var}=1) and 'GDS-15' (OR 1.6, 90% range=0, p_{var}=1). GPs vary in the way they assessed their patients' vulnerability in the functional domain (IADL: median OR 2.8, 90% range 1.6, p_{var}<0.001, BADL: median OR 2.4, 90% range 2.9, p_{var}<0.001) and the social domain (DJG: median OR 1.2, 90% range=1.2, p_{var}<0.001).

Conclusions

GPs seem to share a medical concept of vulnerability, since they take somatic and psychological characteristics uniformly into account in the vulnerability-assessment of older persons. In the functional and social domains, however, variability was found. When more uniformity could be achieved vulnerability assessment by GPs might be a promising instrument to select older people for geriatric care.

INTRODUCTION

In aging societies the prevalence of vulnerability increases.[1] The vulnerable older population is described as the group of older people that presents the most complex and challenging problems to physicians and other healthcare professionals. Older persons often require geriatric care.[2] Vulnerability is a term widely used in discussions on older people, in policy documents and in daily care. The term vulnerability indicates a heterogeneous group of older people with multiple chronic conditions and/or loss of function in one or more domains (e.g. functional, somatic, psychological and social domains).[3;4]

Although various tools to screen for manifestations of vulnerability have been developed,[5-11] no standardized and valid method to assess vulnerability is currently available. Nevertheless, physicians, especially general practitioners (GPs), appear to be able to work with an implicit concept of vulnerability.[12;13]

However, it is unknown whether these implicit concepts of vulnerability are uniform. GPs may share a unique perspective on what defines vulnerability, but may also have distinct perspectives on vulnerability. If and when the vulnerability concepts of GPs appear to be identical, assessment by GPs can be a promising instrument to select older people for specific geriatric care, because such assessment is relatively simple, fast and inexpensive. Therefore, the present study investigates the variability between GPs in their vulnerability assessment of older people, to determine whether GPs share a uniform concept of vulnerability.

MATERIALS AND METHODS

Study design and recruitment

The present analysis is embedded in the Integrated Systematic Care for Older People (ISCOPE) study, a cluster-randomized controlled trial to investigate the effect of proactive care for patients aged 75 years and over. During the inclusion period (September 2009-September 2010), all patients aged ≥75 years in the participating practices received an invitation (by mail) from their GP to participate in the study. Excluded from the study were persons with a terminal illness or a life expectancy of ≤3 months. Participants were asked to complete a postal screening questionnaire for complex health problems on four domains of health (functional, somatic, psychological and social); the questionnaire was sent together with the invitation. Written informed consent was obtained from all participants. Based on the outcomes of the questionnaire, a random sample of the study

population was interviewed at home to obtain baseline data on sociodemographic, functional, somatic, psychological and social characteristics.

The Medical Ethical Committee of the Leiden University Medical Center approved the study. The study was registered in the Netherlands Trial Register (NTR1946).

Primary outcome

Before sending the questionnaires to the patients, GPs were asked to assess the vulnerability of all their patients aged ≥75 years in three categories: i) not vulnerable, ii) possibly vulnerable, and iii) vulnerable. Since our goal was to assess patient vulnerability as defined by the GPs themselves, GPs were not provided with a specific definition of vulnerability. Instead, they were asked to indicate 'in their opinion' which of their patients were considered vulnerable in the context of this study.

Determinants

GP characteristics
From all GPs we collected information on personal characteristics (sex and age), practice characteristics [practice type (single-handed or group), urbanization level (rural or urban)] and characteristics of their older patients (number of patients aged ≥75 years, median age of patients, and percentage of males).

Patient characteristics
From interviews during home visits we obtained information on sociodemographic characteristics (age, sex, income, living situation and home situation). In addition, the presence of problems in four domains of health was assessed with questionnaires.

In the *functional* domain, disability was assessed with the Groningen Activity Restriction Scale (GARS) questionnaire[14;15] which assesses disabilities in competence in nine instrumental activities in daily living (IADL) and in nine basic activities in daily living (BADL). Scores on the IADL and BADL range from 9-36 points with higher scores indicating poorer performance.

In the *somatic* domain information was assessed on self-reported polypharmacy (i.e. taking at least four drugs) and on the medical history covering 17 diseases: diabetes mellitus, heart failure, obstructive lung disease, incontinence, arthritis, osteoporosis, dizziness and falls, prostate problems, cognitive decline, hearing disorder, visual disorder and (a history of) stroke, malignancy, fracture, myocardial infarction, depression and anxiety.

In the *psychological* domain cognitive function was evaluated with the Mini-Mental State Examination (MMSE);[16] scores range from 0-30 points with lower scores indicating poorer cognitive performance. Depressive symptoms were assessed with the 15-item Geriatric Depression Scale (GDS-15)[17] which is specifically developed to screen for depressive symptoms in older people; scores range from 0 (optimal) to 15 points.

In the *social* domain, the De Jong-Gierveld Loneliness Scale (DJG) was used to assess feelings of loneliness, with higher scores (range 0-11) indicating more severe loneliness.[18;19] The GDS-15 and the DJG were restricted to those with a MMSE score of 19 or higher.

Statistical analysis

To describe the GPs' personal/practice characteristics and patient populations, the median and interquartile range (IQR) was calculated of their total population aged ≥75 years.

For the analysis of vulnerability, the assessments by GPs were dichotomized into 'not/possibly vulnerable' and 'vulnerable'. The outcome 'unknown' (2.6% of the total population) was handled as missing data.

In the populations assessed as 'not/possibly vulnerable' or 'vulnerable' the association between GP characteristics and percentage of vulnerable older persons per GP was examined. The median percentage (IQR) of vulnerable older persons per GP characteristic was calculated and differences analyzed with the Mann-Whitney U-test. To describe the characteristics of the sample that was visited at home, characteristics of the 'not/possibly vulnerable' and 'vulnerable' persons were compared by testing differences in medians (IQR) for continuous variables with the Mann-Whitney U-test, and differences in proportions for dichotomous variables with Pearson's chi-square test.

To investigate the association between patient characteristics and the patient's chance to be assessed as vulnerable, we applied mixed effects logistic regression on the participants visited at home and who were assessed as 'not/possibly vulnerable' or 'vulnerable'. To adjust for the intra-class correlation within the practices a random intercept was used. The strength of an association was expressed by the odds ratio (OR) for dichotomous variables and by the OR per standard deviation (SD) for continuous variables. If one GP gives more weight to a characteristic than another GP, the ORs will vary between GPs. To investigate whether the OR for a certain characteristic varies between GPs, a subsequent analysis was performed in which we extended the random intercept model with an extra random term for that characteristic, thereby allowing that every GP has his/her own OR.

The model assumes a lognormal distribution for the GP-specific ORs. The median and 90% reference interval of this distribution were estimated. The reference interval runs from the 5th to the 95th percentile of the distribution and contains the ORs of 90% of the GPs, thereby serving as a characterization of the variability between GPs in the weight they attribute to a patient characteristic in assessing vulnerability. If the GPs do not vary in their assessment, their ORs will be the same and there will be no range around the median OR. If the GPs vary in their assessment and the range includes OR=1, some GPs will weigh a patient characteristic in a direction opposite to that of other GPs. P-values for variability (p_{var}) are calculated with the log-likelihood ratio test.

All analyses were performed with IBM SPSS Statistics version 20.

RESULTS

Study population and vulnerability assessment

In total, 77 GPs in 55 participating general practices worked for 11392 registered patients aged 75 years and over. Table 1 presents the baseline characteristics of these 77 GPs. Their median age was 51.4 (IQR 43.1 to 57.1) years and 46 (59.7%) were male. The majority of the GPs (77.9%) worked in an urban environment. The number of registered patients aged ≥75 years per GP ranged from 12 to 479 with a median of 131 (IQR 66 to 210). Of the 11392 eligible patients, the GPs completed the assessment for 10361

Table 1. Personal and practice characteristics of GPs (n=77) and the characteristics of their registered population aged 75 years and over.

	n (%) or median (IQR)
Characteristics of general practitioner (n=77)	
Age in years	51.4 (43.1-57.1)
Sex (male)	46 (59.7)
Environment (urban)	60 (77.9)
Type of practice (single-handed)	24 (31.2)
Characteristics of the population per GP	
Number of persons aged 75 years and over	131 (66-210)
Median age of the population	80.8 (79.8-82.1) *
Percentage male in the population aged 75 years and over	36.4 (31.9-40.0)†
Percentage vulnerable older persons‡	32.0 (19.5-40.1)†

*median (IQR) of the median ages per GP-population
†median (IQR) of the percentages per GP-population
‡calculated for 10361 people who were assessed by the GP as not vulnerable/possibly vulnerable/vulnerable

patients. Of the latter group, 2848 (27.5%) were rated as vulnerable, 2644 (25.5%) as possibly vulnerable, and 4869 (47.0%) as not vulnerable. Of the remaining 1031 persons, 292 were assessed as 'unknown' and 739 assessments were missing (reasons for missing: 53 persons died, 123 persons moved away, 71 persons were sent to a nursing home, 61 persons were terminally ill, 52 persons were excluded for other reasons, and 379 were missing for unknown reason). Overall, the median percentage of vulnerable patients per GP was 32.0% (IQR 19.5 to 40.1%), ranging from 2.4% to 81.0%.

GPs living in an urban environment assessed a higher percentage of their patients as vulnerable than GPs in a rural environment (33.3% (IQR 22.1 to 40.9%) vs. 23.6% (IQR 8.4 to 37.4%), p=0.044). No differences in vulnerability assessment were found for the type of practice, for the GPs' personal characteristics (age and sex) and for the number of persons aged ≥ 75 years in their practice (all p>0.05) (Table 2).

Of the 10361 patients assessed by the GPs, a questionnaire was sent to 10078 patients (excluding: 48 persons who died, 101 persons too ill, 55 persons in a nursing home, 25 persons who did not understand Dutch, and 54 persons were excluded by the GP for other reasons). Of these, 6518 (64.7%) persons responded to the questionnaire (reasons for non-participation: 2690 refused, 813 did not respond, 39 moved away, and 18 for other unknown reasons).

Based on the outcomes of the questionnaire, a sample of 2828 persons was visited at home. Table 3 presents the characteristics of these persons of whom 31.6% (n=894) were

Table 2. Association between characteristics of 77 GPs and the percentage of vulnerable older persons per practice (n=10361).

Characteristics of GPs and their practice		n	Median percentage of vulnerable older persons (IQR)	p-value*
GPs' age	≤ 50 years	35	35.7 (23.5-43.2)	0.091
	> 50 years	42	28.8 (15.5-38.4)	
GPs' sex	Male	46	32.0 (19.7-38.8)	0.705
	Female	31	33.3 (19.1-40.8)	
Environment	Urban	60	33.3 (22.1-40.9)	0.044
	Rural	17	23.6 (8.4-37.4)	
Type of practice	Single-handed	24	26.2 (10.5-35.7)	0.052
	Group	53	33.6 (22.8-40.8)	
Total number of 75-plus persons in practice	≤ 130 persons	38	34.2 (22.2-42.9)	0.121
	> 130 persons	39	30.2 (16.1-36.4)	

*Mann-Whitney U-test

assessed as vulnerable and 68.4% (n=1934) as not/possibly vulnerable. The participants assessed as vulnerable were older, i.e. median age 83 years (IQR 80 to 88 years) vs. 81 years (IQR 78 to 86) (p <0.001) and were more often living in a residential home (15.4% vs. 7.8%) (p <0.001). In all health domains (functional, somatic, psychological and social) the vulnerable older people had less favorable scores than the not/possibly vulnerable persons (all p <0.001).

Table 3. Association between patient characteristics and vulnerability assessment by the GP (n=2828).

	Vulnerability by GP		p-value*
	Yes (n=894) n (%) or median (IQR)	**Not/possibly (n=1934) n (%) or median (IQR)**	
Socio-demographic factors			
Age	83 (80-88)	81 (78-86)	<0.001
Sex, male	294 (32.9)	598 (30.9)	0.296
Income, low (only state pension)†	146 (16.4)	273 (14.1)	0.116
Living situation, living alone†	580 (64.9)	1204 (62.3)	0.184
Home, residential†	138 (15.4)	150 (7.8)	<0.001
Functional domain			
IADL†	27 (20-33)	19 (13-25)	<0.001
BADL†	11 (9-17)	9 (9-11)	<0.001
Somatic domain			
Total number of self reported diseases	5 (3-6)	4 (2-5)	<0.001
Self reported poly-pharmacy (≥ 4 drugs)†	673 (75.7)	1143 (59.2)	<0.001
Psychological domain			
MMSE†	27 (24-29)	28 (26-29)	<0.001
GDS-15†‡	2 (1-4)	1 (0-3)	<0.001
Social domain			
DJG†‡	3 (1-5)	2 (0-4)	<0.001

*Mann-Whitney U-test for continuous variables or Pearson's chi-square test for dichotomous variables
IADL = Instrumental Activities in Daily Living, BADL=Basic Activities in Daily Living, MMSE=Mini-Mental State Examination, GDS-15= 15-item Geriatric Depression Scale, DJG= De Jong-Gierveld Loneliness Scale
† missing in 1-38 participants
‡not administered in 149 participants

Table 4. Variability in the influence of patient characteristics on the vulnerability assessment by the GP (n=2828).

Patient characteristics	SD*	OR		Variability			Median OR and 90% range
		median	p-value	variance	p_{var}	5-95% OR (90% range)	
Sociodemographic factors							
Age	5.24	1.6	<0.001	0.015	<0.001	1.3-1.9 (0.6)	
Sex, male	-	1.1	0.337	<0.001	1	1.1-1.1 (0)	
Income, low (only state pension)	-	1.2	0.241	0.138	0.033	0.64-2.2 (1.6)	
Living situation, living alone	-	1.1	0.438	0.210	0.144	0.51-2.3 (1.8)	
Home, residential	-	2.7	<0.001	0.117	0.017	1.5-4.7 (3.2)	
Functional domain							
IADL	8.27	2.8	<0.001	0.033	<0.001	2.1-3.7 (1.6)	
BADL	4.87	2.4	<0.001	0.118	<0.001	1.4-4.3 (2.9)	
Somatic domain							
Total number of self reported diseases	2.27	1.7	<0.001	<0.001	1	1.7-1.7 (0)	
Self reported poly-pharmacy (≥ 4 drugs)	-	2.3	<0.001	<0.001	1	2.3-2.3 (0)	
Psychological domain							
MMSE	3.57	1.9	<0.001	0.016	<0.001	1.5-2.3 (0.8)	
GDS-15	2.56	1.6	<0.001	<0.001	1	1.6-1.6 (0)	
Social domain							
DJG	2.81	1.2	0.005	0.078	<0.001	0.75-1.9 (1.2)	

*Standard deviation (SD) is calculated for continuous data. The Odds Ratio (OR) is estimated per SD decline in functioning

IADL = Instrumental Activities in Daily Living, BADL=Basic Activities in Daily Living, MMSE=Mini-Mental State Examination, GDS-15= 15-item Geriatric Depression Scale, DJG= De Jong-Gierveld Loneliness Scale

Variability between GPs in vulnerability assessment

To investigate the variability between GPs in the weight they attribute to a patient characteristic in assessing vulnerability, data of the 2828 participants visited at home were analyzed (Table 4).

In the sociodemographic domain, GPs only used age and residential living in their vulnerability assessment and differed in the weight they attributed to these factors (median OR 1.6, 90% range=0.6, p_{var} <0.001 and median OR 2.7, 90% range=3.2, p_{var}=0.017, respectively). Variability was also found between GPs in the functional domain (IADL: median OR 2.8, 90% range=1.6, p_{var} <0.001 and BADL: median OR 2.4, 90% range=2.9, p_{var} <0.001). No variability was found in the somatic domain (self-reported diseases median OR 1.7, 90% range=0, p_{var}=1, polypharmacy median OR 2.3, 90% range=0, p_{var}=1). In the psychological domain variability was also absent for depressive symptoms (GDS-15: median OR 1.6, 90% range=0, p_{var}=1), but GPs differed in the weight they attributed to cognition (MMSE: median OR 1.9, 90% range=0.8, p_{var} <0.001). In the social domain, variability was found between GPs and they also differed in the direction of the association with vulnerability: i.e. some GPs gave a positive and others a negative weight to loneliness (DJG: median OR 1.2, 90% range=1.2, p_{var} <0.001).

DISCUSSION

Principle findings

This study investigated the variability in vulnerability assessments by GPs. The percentage of older patients assessed as 'vulnerable' by the GP varied per practice (median 32.0%, IQR 19.5 to 40.1%, range 2.4 to 81.0%). This variation was not only due to differences in the patient-populations of the GPs, but also depended on differences in the weight GPs attributed to some patient characteristics in the vulnerability assessment. All GPs took some somatic and psychological characteristics uniformly into account. In the functional and social domains variability was found in the way GPs assessed their patients' vulnerability.

In the present study, an urban environment was the only practice characteristic that was associated with the percentage of vulnerable older persons. However, the environment of the GP's practice can also be considered as a patient characteristic. Apparently, older persons living in a city were more likely to be assessed as 'vulnerable'.

In the somatic and psychological domains, patient characteristics predicted the vulnerability assessment by the GP, and the GPs weighed these patient characteristics almost

equally. The formal education of GPs and their corresponding focus on diseases may explain these findings. GPs are educated in clinical observation, which mainly takes into account somatic and psychological characteristics, as well as age and sex. This study shows that (with the exception of sex) GPs almost uniformly attribute predictive values to these items; sex did not predict the outcome of the vulnerability assessment and no differences were found between GPs. Apparently, sex is not a discriminative factor in the vulnerability assessment by GPs.

In the functional domain, although strong predictive values of the patient characteristics were found, GPs differed in the way they used these patient characteristics in their assessment. Although GPs are aware of the importance of functional status for vulnerability, they might not use a standard approach while taking functioning into account. Similar results were found for type of residence: this might be explained by the fact that people in residential homes often have a functional impairment. In clinical practice, GPs tend to focus on medical problems using a disease model as concept of care. If the vulnerability assessment would have been carried out, for example, by nurses (who are mainly trained in functional models), it is likely that uniform outcomes will be found in the functional domain and variability in the somatic domain. If GPs received more training in the use of functional models,[20] the differences between them might become smaller.

Finally, in the social domain the loneliness score predicted vulnerability, even though GPs varied in the way they took this characteristic into account: i.e. loneliness increased a patient's chance to be assessed as vulnerable by most GPs, whereas some GPs weighed loneliness in the opposite direction. Interpretation of this outcome is difficult but might indicate that GPs are unaware of patients' loneliness as measured in the present study; this is in line with earlier research indicating that some GPs rarely ask their patients about loneliness.[21] The impact of the social domain on vulnerability should be explored in further studies.

Comparison with existing literature

Various tools have been developed to screen for vulnerability,[5-11] but no standardized and valid method is available. Knowledge on the prevalence of vulnerability as assessed by GPs is currently limited. For example, although Hoogendijk et al. compared clinical judgment with several frailty instruments, only one GP was involved.[22] To our knowledge, ours is the first study in which several GPs were asked to assess the vulnerability of their registered older patients, without imposing a pre-described definition. The present study shows that GPs generally share a unique perspective on what defines vulnerability in the somatic and psychological domain, but differ in the way they interpret

the functional domain. GPs are probably not aware of this phenomenon, because other studies report that they consider themselves able to work with an undefined concept of vulnerability.[12;13]

Strengths and limitations

The present study has several strengths. It is a large population-based study of GPs and their registered patients aged ≥ 75 years. Also, because we did not impose a definition of 'vulnerability', the assessment revealed the GP's own interpretation of the concept of vulnerability. In this study, 77 GPs assessed the vulnerability of almost all of their patients; therefore, there was no (or minimal) selection of patients in the assessment by the GP. Furthermore, GPs were unaware of the outcome of the study measurements because they performed the assessments before randomization and before other data were collected. Unfortunately, it was not possible to interview the GPs about the concepts of vulnerability they used during their assessments. However, we were able to analyze the variability between GPs in the way they weighed the characteristics of their patients. In this study the variability between GPs might be an overestimation of the true variability, because the most obviously vulnerable patients may not have been included in our analysis. Variability can also partly be explained by the fact that GPs might not have examined all their patients recently. At the moment of assessing their patients' vulnerability, GPs were unable to take all recent changes in patients' functioning into account. Moreover, other patient characteristics that might influence the vulnerability assessment may not have been examined. However, the literature does not include any other important characteristics that we did not investigate.

Implications and further research

GPs appear to share a medical concept of vulnerability because they take somatic and psychological characteristics uniformly into account in the vulnerability assessment; however, they differ in the weight they attribute to functional status and loneliness. More uniformity might be achieved if GPs received training in the use of a functional model as concept of care. The impact of the social domain on vulnerability should be explored in further studies. More research is needed to compare the outcomes of the vulnerability assessment by GPs with those of other tools that measure vulnerability. Such analyses may reveal the additional value of screening tools compared to assessment by GPs, which is a simple, inexpensive and apparently reliable method. If stratification on vulnerability becomes feasible, this will facilitate the selection of older individuals who may best benefit from specific geriatric care.

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Chapter 5

Assessment of appropriateness of screening community-dwelling older people to prevent functional decline

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ABSTRACT

Objectives

To identify appropriate screening conditions, stratified according to age and vulnerability, to prevent functional decline in older people.

Design

A RAND/University of California at Los Angeles appropriateness method.

Setting

The Netherlands.

Participants

A multidisciplinary panel of 11 experts.

Measurements

The panelists assessed the appropriateness of screening for 29 conditions mentioned in guidelines from four countries, stratified according to age (60–74, 75–84, ≥85) and health status (general, vital, and vulnerable) and received a literature overview for each condition, including the guidelines and up-to-date literature. After an individual rating round, panelists discussed disagreements and performed a second individual rating. The median of the second ratings defined the appropriateness of screening.

Results

The panel rated screening to be appropriate in three of the 29 conditions, indicating that screening was expected to prevent functional decline. Screening for insufficient physical activity was considered appropriate for all three age and health groups. Screening for cardiovascular risk factors and smoking was considered appropriate for the general and vital population aged 60 to 74. Of the 261 ratings, 63 (24%) were classified as uncertain, of which 42 (67%) concerned the vulnerable population. The panelists considered conditions inappropriate mainly because of lack of an adequate screening tool or lack of evidence of effective interventions for positive screened persons.

Conclusion

The expert panel considered screening older people to prevent functional decline appropriate for insufficient physical activity and smoking and cardiovascular risk in specific groups. For other conditions, sufficient evidence does not support screening. Based on their experience, panelists expected benefit from developing tests and interventions, especially for vulnerable older people.

INTRODUCTION

The interest in screening community-dwelling older people is increasing,[1-4] and several guidelines for such screening have been issued.[5-13] Screening is a strategy used in a population to detect a disease, risk factor, or ailment in individuals with unrecognized signs or symptoms. In general, the intention of screening is to identify the screened condition early, enabling earlier intervention and management to postpone diseases and death, but older people (especially frail older people) do not always benefit from screening because of their shorter natural life expectancy and their lack of physiological reserve to tolerate the invasive interventions called for after screening.[4]

For these older populations, screening can have an additional aim. In this age group, the aim is also to contribute to healthy aging, which is a prominent theme in current health policy.[14-17] Healthy aging is not only a matter of maintaining good physical and mental health, but also of older people remaining independent and participating in social activities. As the general health status of older people declines, values such as functioning in daily life and well-being become more important than life expectancy.[18] Therefore, it was postulated that a screening approach to community-dwelling older people would be appropriate if it aimed at preventing and postponing functional decline,[19] but current screening guidelines tend to ignore this aim. In addition, specific research on screening in older people is scarce. Therefore, screening guidelines often have to address a lack of age-specific evidence.

In the present study, an expert panel assessed the contribution of screening of community-dwelling older people to the prevention of functional decline using the RAND/University of California at Los Angeles (UCLA) appropriateness method.[20-22] This method was chosen because a preceding literature search showed that the available scientific evidence was inconclusive. This RAND/UCLA appropriateness method was specifically developed to combine the available scientific evidence with the collective judgment of experts. To select conditions for this study, the content of general guidelines and protocols on screening and prevention was used. The appropriateness of screening the older population to prevent functional decline was assessed for several conditions by applying the most frequently used criteria for screening of this older population, formulated in 1968 by Wilson and Jungner (Table 1).[23] Because the older population is heterogeneous, and it was hypothesized that age and vulnerability would be important determinants in assessing appropriateness, the present study stratified according to age[24] and vulnerability.[25,26]

METHODS

The RAND/UCLA appropriateness method was used.[20,22] The method was designed in the mid-1980s, primarily as an instrument to enable measurement of the overuse and underuse of medical and surgical procedures. Since then, this method has been used for many topics and its validity and reliability have been demonstrated in a wide variety of medical and preventive procedures that lack a firm evidence base.[27-29] For a detailed description see Appendix.

Selection of screening conditions and literature review

Guidelines and protocols on screening and prevention were used to select conditions for this study. Conditions were selected from three Dutch guidelines and protocols on screening and prevention[5-7] and from English-language guidelines of five leading healthcare institutes in the United States, Australia, and Great Britain.[8-13] Two of these documents were specifically developed for vulnerable older people,[6,10] but none of them was specifically aimed at prevention of functional decline.

A screening condition was considered eligible if it was recommended in one or more of these guidelines; this resulted in 29 conditions. To compile an overview of the evidence for each of these conditions, the guidelines and the literature references on which these guidelines were based were collected. For each condition separately, a scientist with expertise in the content of that condition was asked to comment on the guidelines and reference lists and to add up-to-date information if available. These files, one for each condition, formed the evidence package for the expert panel. The panelists used the literature overview from the evidence packages and their expertise to weigh the evidence for screening of each condition.

To acquire an overview of the differences between the guidelines and protocols, two researchers (YD, VvdM) independently divided the screening recommendations of the guidelines into the following groups: positive advice for older people in general, positive advice for specific groups of older people (people at risk, as defined in the guidelines), negative advice, insufficient evidence to give advice, or screening not mentioned in the guideline. Any disagreement between the two researchers was settled by consensus discussions or by a third party (JG).

Expert panel and rating process

For the panel, 11 experts from disciplines involved in geriatric care and screening were recruited from eight university medical centers: seven physicians with scientific expertise, of whom four were general practitioners (JD, JM, HS, AW), two were clinical geriatri-

cians (SdR, RW), and one was a nursing home physician (KdV); three scientists, of whom two were public health scientists (MG, FS), and one was a nursing scientist (MS); and an expert from Vilans, a Dutch Knowledge Centre on Ageing (RvO). In brief, the RAND/UCLA appropriateness method entails two rounds of independent ratings by panelists, with one face-to-face group discussion (supervised by an independent chairman) between these rounds.[22] The panelists rated the appropriateness of screening for each condition. The score of each panelist was equally weighed in the final ratings. One month before the meeting, panelists received the evidence packages, definitions of the terms used for the procedure, the criteria of Wilson and Jungner,[23] and the rating sheets.

In accordance with the RAND/UCLA appropriateness method, the expert panel was instructed to weigh evidence and to use their expert opinion for assessment of the contribution of screening to the prevention or postponement of functional decline for each specific condition. The panelists followed the previously developed criteria of Wilson and Jungner for each condition; they investigated whether evidence was present to fulfill the criteria for a specific condition, taking their expert opinion about a potential benefit into account.

Prevention or postponement of functional decline was defined as supporting the ability of older people to function as independently as possible.[18] Screening was considered appropriate if the health benefits exceed the health risks by a margin that was sufficiently wide to make the procedure worth doing.[20,22,30] The expert panel was asked to rate each condition for each of the three age groups (60–74, 75–84, ≥85) and for each of the three levels of health status (general, vital, and vulnerable).

Table 1. Wilson and Jungner criteria for screening.[23]

1.	The condition sought should be an important health problem
2.	There should be an accepted treatment for patients with recognized disease
3.	Facilities for diagnosis and treatment should be available
4.	There should be a recognizable latent or early symptomatic stage
5.	There should be a suitable test or examination
6.	The test should be acceptable to the population
7.	The natural history of the condition, including development from latent to declared disease, should be adequately understood
8.	There should be an agreed policy on whom to treat as patients
9.	The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole
10.	Case-finding should be a continuing process and not a 'once and for all' project

In the present study, the general population was defined as the overall older population. This population was split into a vulnerable population with a high prevalence of diseases and disorders, a poorer prognosis, disability of various kinds, multiple problems simultaneously, and a vital population that was defined as nonvulnerable.

The rating process resulted in nine ratings per condition. Rating was done on a 1- to 9-point Likert scale (1 = extremely inappropriate, 5 = uncertain or equivocal, and 9 = extremely appropriate to screen).

The rating sheets were returned by mail and tabulated, and the results of the first-round rating were used to guide a subsequent 2-day face-to-face meeting of all panelists in March 2009. At the face-to-face meeting, headed by a moderator experienced in the RAND/UCLA appropriateness method (HR),[6,31] each panelist received a report of his or her own first-round ratings, a frequency distribution, and the median of the whole panel. The individual ratings were blinded to other group members. Every condition was discussed to identify areas of disagreement, to highlight evidence not cited in the literature reviews, and to clarify specific definitions or wording of the conditions. In addition, panelists could revise existing conditions to better fit their judgment and could propose new conditions. The Wilson and Jungner criteria were used as leading principles in the discussion. After these discussions, in which the assessment was based on the combination of evidence and expert opinion, each panelist rerated all of the conditions on the 1- to 9-point scale. The entire discussion was audiotaped, and two researchers (YD, JG) made field notes. After the session, a report was written and sent to the panelists for their comments. These documents were used in the analysis to explain the outcomes of the ratings.

Appropriateness

The final appropriateness judgments were based on the median panel rating and level of disagreement for each condition in the second round, using the following definitions: all conditions with a median rating of 7 to 9, rated without disagreement, were classified as appropriate; those with a median rating of 1 to 3, rated without disagreement, were classified as inappropriate; and those with a median rating of 4 to 6, as well as all conditions rated with disagreement, regardless of the median, were classified as uncertain. A condition was considered to be rated with disagreement when at least three panelists rated it in the 1 to 3 range, and at least three panelists rated it in the 7 to 9 range.[32]

RESULTS

Recommendations by guidelines

The guidelines for screening[5-13] showed a great variety of conditions and screening advice. None of the individual 29 conditions was addressed in all screening guidelines. The most frequently advised screening was for smoking status, followed by cardiovascular risk factors, malnutrition, and overweight. For abdominal aortic aneurysm, cognitive impairment, depression and anxiety, diabetes mellitus, and osteoporosis, the guidelines gave conflicting recommendations; some advised screening for these conditions, whereas others warned against screening. Table 2 gives an overview of the recommendations in the guidelines; the conditions included in the second rating process are also shown.

RAND/UCLA appropriateness method

In the first round with 29 conditions, there was disagreement in 23% (59/261) of the ratings. In the second round, after the face-to-face meeting, the disagreement was reduced to 3.4% (9/261). During the discussion sessions, three conditions were dropped because they were too difficult to define in an unequivocal way (social well-being, social support, and spare time), two conditions were divided into two parts (nutrition into malnutrition and undernutrition and burden of the informal caregiver into burden of the screened person as informal caregiver and burden of the informal caregivers around the screened person). One specification of a subgroup was added to abdominal aortic aneurysm and was discussed separately (abdominal aortic aneurysm in (ex-)smoking men). As a result, the second round also addressed 29 conditions.

Appropriateness

For the older population in general, screening for insufficient physical activity for all three age groups and screening for cardiovascular risk and smoking for aged 60 to 74 were rated appropriate, indicating that screening was expected to prevent functional decline (Table 3). Screening was rated uncertain for hearing impairment (all three age groups), colorectal cancer (60–74 and 75–84), the burden of the screened person as informal caregiver, smoking status (75–84 and ≥85), cardiovascular risk factors (75–84) and abdominal aortic aneurysm in (ex-)smoking men (60–74), indicating serious doubts. For all the other conditions, screening of the general older population was considered inappropriate.

Influence of vulnerability

Screening for insufficient physical activity was considered appropriate for all older persons (Table 3). Cardiovascular screening and screening for smoking status were rated

Table 2. Screening conditions for older persons in the guidelines.

Conditions	Preventive activities in general practice[13] (Australia)	U.S. Preventive Services Task Force[12] (United States)	ICSI: Preventive services for adults or Primary prevention of chronic disease risk factors[8,9] (United States)	National screening committee[11] (Great Britain)	ACOVE-3 US (vulnerable elder)[10] (United States)	ACOVE-NL (vulnerable elder)[6] (The Netherlands)	Practice guidelines Dutch College of General Practitioners[5] (The Netherlands)	Vilans: Preventive health care centers for older people, guidebook[7] (The Netherlands)
Abdominal aortic aneurysm	-	+	+	-	+	0	0	0
Abdominal aortic aneurysm in (ex-) smoking males	-	+	+	-	+	0	0	0
Alcohol misuse	++	++	++	0	+	0	0	++
Burden of informal caregivers around the screened person	+	0	0	0	0	0	0	0
Burden of the screened person as informal caregiver	0	0	0	0	0	0	0	++
Cardiovascular risk	++	++	++	++	0	0	+	++
Chronic kidney disease	++	0	0	0	0	0	0	0
Cognitive impairment or dementia	-	?	?	0	+	+	0	0
Colorectal cancer	++	++	++	0	+	0	0	0
Depression and anxiety	-	++	++	0	+	?	0	++
Diabetes mellitus	++	+	-	0	-	0	+	++
Falls	++	0	?	0	+	?	0	++
Functional status	0	0	0	0	+	0	0	++
Hearing impairment	++	0	++	0	+	0	0	++
Insufficient physical activity	++	?	++	0	+	0	0	++
Loneliness	0	0	0	0	0	0	0	++

Table 2. (Continued)

Conditions	Preventive activities in general practice[13] (Australia)	U.S. Preventive Services Task Force[12] (United States)	ICSI: Preventive services for adults or Primary prevention of chronic disease risk factors[8,9] (United States)	National screening committee[11] (Great Britain)	ACOVE-3 US (vulnerable elder)[10] (United States)	ACOVE-NL (vulnerable elder)[6] (The Netherlands)	Practice guidelines Dutch College of General Practitioners[5] (The Netherlands)	Vilans: Preventive health care centers for older people, guidebook[7] (The Netherlands)
Malnutrition	++	+	++	0	+	0	+	++
Osteoporosis	++	+	++	-	+	0	-	++
Overweight	++	++	++	0	+	0	+	++
Pain	0	0	0	0	+	0	0	++
Polypharmacy	0	0	0	0	+	+	0	++
Skin cancer	+	?	?	0	0	0	0	0
Sleep disorders	0	0	0	0	+	0	0	++
Smelling problems	0	0	0	0	0	0	0	++
Smoking status	++	++	++	++	+	0	+	++
Speech problem	0	0	0	0	0	0	0	++
Undernutrition	0	0	0	0	+	?	0	++
Urinary incontinence	+	0	0	0	+	0	0	++
Visual impairment	++	?	++	0	+	0	0	++

++ = screening for older people recommended; + = screening for older people at risk recommended (including vulnerable elderly); - = advice against screening;
? = insufficient evidence for or against; 0 = screening not a topic.
ACOVE = Assessing Care of the Vulnerable Elders.

appropriate in the vital population aged 60 to 74. Uncertainty (median range: 4–6 or disagreement) about the appropriateness was rated in 24% (63/261) of the scores. Of all uncertain outcomes, 67% concerned the vulnerable population. The panelists argued that lack of sufficient evidence to fulfill the criteria of Wilson and Jungner is mainly due to lack of research in this population as such. Based on their expertise in clinical practice, they assumed that development of specific tests and interventions for this group may generate evidence and will lead to benefits of screening, especially when the screening approach is embedded in regular care.

Influence of age

In contrast to expectations, the age category of the persons did not strongly influence the ratings of the panel (Table 3). Exceptions to this were cardiovascular screening and smoking status (influence of age in all three groups of health status); abdominal aortic aneurysm in (ex-)smoking men, colorectal cancer, burden of the screened person as informal caregiver (influence of age in the general and vital population); and urinary incontinence (influence of age in the vital population). For cardiovascular screening of older people, the main problem is lack of a suitable test. The panelists considered that Framingham Study scores were not valid for the older age categories because these scores do not predict cardiovascular mortality in the oldest old.[33] For smoking, abdominal aortic aneurysm in (ex-)smoking men, and colorectal cancer, the importance of screening declines with increasing age for different reasons (e.g., for smoking, there is insufficient evidence for the yield of stopping at older age; for aneurysm, the risk of a surgical procedure increases with age; and for colorectal cancer, the natural history at older age is unknown, and the risk of surgery increases with age). In contrast, the appropriateness of screening for urinary incontinence and for the burden of the screened person as informal caregiver increases with age, mainly because the yield increases.

Reasons for uncertainty and inappropriateness

When the panelists expected benefits of screening according to their expert opinion, although evidence was lacking, they rated the condition in the uncertain range. Screening for a condition was rated in the inappropriate range when evidence from literature was against screening or when evidence was lacking and the panelists expected no benefit according to their expert opinion. In the panel discussions, the most frequently used argument for inappropriateness was lack of evidence for effective interventions (Wilson and Jungner criterion 2).[23] There was sometimes a perceived lack of a rational evidence-based intervention (e.g., dementia, smelling problems), and sometimes it was assumed that adherence to advice or treatment after a positive screening would be too low on the basis of experience or circumstantial scientific evidence (e.g., urinary incontinence, hearing aid, alcohol abuse). Furthermore, the panel thought some conditions to

Table 3. Appropriateness of screening to prevent functional decline in the general older population, vital older persons and vulnerable older persons, stratified according to age.

Conditions to screen for*	Final rating, (median)†								
	General older population			Older persons					
				Vital			Vulnerable		
	60-74	75-84	≥ 85+	60-74	75-84	≥ 85+	60-74	75-84	≥ 85+
At least one rating appropriate									
Insufficient physical activity	7	7	7	7	7	7	7	7	7
Smoking status	7	6	4	7	6	4	6	5	3
Cardiovascular risk	7	3D‡	2	7	5D	2	4D	2	2
At least one rating uncertain									
Burden of the screened person as informal caregiver	3	4	4	3	4	4	5	5	5
Hearing impairment	4	4	4	2	2	2	5	5	5
Urinary incontinence	3	3	3	3	4	4	5	5	5
Colorectal cancer	5	4	2	6	5	2	3	3	2
Burden of informal caregivers around the screened person	1	2	2	1	1	2	5D	5D	5D
Cognitive impairment / dementia	2	2	2	1	1	1	5	5	6
Depression and anxiety	2	2	2	2	2	2	5	5	5
Functional status	3	3	3	2	2	2	5	5	5
Loneliness	2	2	2	2	2	2	5	5	5
Malnutrition	2	2	2	2	2	2	4D	4D	4D
Pain	2	2	2	1	1	1	5	5	5
Polypharmacy	2	2	2	2	2	2	5	5	5
Undernutrition	3	3	3	2	2	2	5	5	5
Visual impairment	2	2	2	2	2	2	6	6	6
Abdominal aortic aneurysm in (ex-) smoking males	4	2	2	5	3	2	2	2	1
All ratings inappropriate									
Abdominal aortic aneurysm	2	1	1	2	1	1	1	1	1
Alcohol misuse	2	2	2	2	2	2	2	2	2
Chronic kidney disease	2	2	2	2	2	2	3	3	3
Diabetes mellitus	3	3	2	3	3	2	2	2	2
Falls	2	2	2	2	2	2	3	3	3
Skin cancer	1	1	1	1	1	1	1	1	1
Osteoporosis	1	1	1	1	1	1	2	2	2
Overweight	2	2	2	3	3	3	2	2	2
Sleep disorders	2	2	2	2	2	2	3	3	3
Smelling problems	1	1	1	1	1	1	1	1	1
Speech problems	1	1	1	1	1	1	1	1	1

* Ranked according to appropriateness and alphabetically.

† Range: 1-3, inappropriate; range 4-6, uncertain ; range 7-9, appropriate.

‡ D = disagreement: at least three panelists rated in the 1-3 range and at least three panelists rated in the 7-9 range.

be of insufficient importance (Wilson and Jungner criterion 1) because the prevalence was too low to warrant screening (e.g., skin cancer in the Netherlands) or the relevance of screening for the condition was not considered to be high enough (e.g., pain and sleeping disorders). In general, the panelists expected that people with these problems and motivation for subsequent interventions would already be seeking help. For some conditions, a suitable test or examination was lacking (Wilson and Jungner criterion 5): too many false positives (fecal occult blood test for colorectal cancer) or too many false negatives (alcohol abuse, osteoporosis), problems with acceptance of the test (colonos-copy), or test not validated for screening (De Jong-Gierveld Loneliness Scale).[34]

DISCUSSION

Principle findings

Despite increasing interest in screening of community-dwelling older people and the recommendations in guidelines, the Dutch panel considered screening of only a few conditions to be appropriate. Screening for insufficient physical activity to prevent functional decline is appropriate for all older persons. Screening for cardiovascular risk factors and smoking status are considered useful for the general older population aged 60 to 74 but not for vulnerable older people in the same age range. There is insufficient evidence to support screening for the other investigated conditions.

During the face-to-face meeting, the experts emphasized that an uncertain or inap-propriate rating does not mean that the condition is irrelevant but that there was insufficient evidence to recommend an active screening approach. To conclude that screening contributes to the prevention of functional decline, screening must at least approximately meet the criteria of Wilson and Jungner. When evidence to fulfill the criteria of Wilson and Jungner was lacking or inconclusive, the experts' opinions about a potential benefit to prevent functional decline were taken into account. It was not thought that strong evidence supported interventions that merely stimulate well-being (e.g., interventions to address loneliness), although based on experience, the panelists expected at least some benefit from these interventions.

Vulnerability was considered to be an important factor in the determination of appro-priateness of screening. For 11 of the 29 conditions, the panelists were uncertain about the appropriateness of screening vulnerable older people, whereas they considered screening of older persons with good vitality for the same condition to be inappropriate. Because of lack of research data on the vulnerable group, the panelists had to rely on their expert opinion to rate these screening options. They expect benefit from screening

when more tests and interventions are developed for this group. Because the majority of vulnerable older people already receive medical care for their chronic disease(s), the panelists expected more benefit from improving regular care than from a separate screening program.

Age played a small role during the panel discussions. Appropriateness of screening was modified according to age for only six conditions: smoking status, cardiovascular risk, abdominal aortic aneurysm in (ex-)smoking men, colorectal cancer, burden of the screened person as informal caregiver, and urinary incontinence. A possible explanation for this is the relationship between age and vulnerability, with the latter being the discriminating factor in rating.

Some guidelines[5,7,11,13] claim that their recommendations are based on the criteria of Wilson and Jungner, although there are marked differences between the recommendations in these guidelines. A possible explanation for the differences in these guidelines is a difference in the validity of the guideline procedures. For example, the Vilans guidebook,[7] which contains the most positive advice, is a descriptive protocol of available screening conditions for older people rather than an evidence-based screening guideline. Also, considerable differences may exist between countries in the interpretation of evidence because of cultural differences and differences in healthcare systems, which influence recommendations in the guidelines.[35] The validity of the guideline processes (e.g., using the Appraisal of Guidelines, Research, and Evaluation in Europe (AGREE) instrument)[36] was not formally assessed in the present study, because the main focus was determination of the appropriateness of screening by the expert panel.

Comparison of the outcome of the RAND/UCLA appropriateness method with the recommendations of the various guidelines shows considerable differences between guidelines. The panel rating was more in accordance with the European guidelines than with the U.S. and Australian guidelines, probably because of an underlying cultural difference; (e.g., when evidence is lacking, Dutch healthcare professionals tend to rely on the adage *primum non nocere*, to defend patients from iatrogenic harm). Vulnerable older people are at higher risk for expected and unexpected side effects of confirmatory testing that follow a screening test and subsequent treatment.[4] In addition, organization of care and healthcare availability may play a role; all inhabitants in The Netherlands have healthcare insurance, and almost everyone is registered with one general practice over many years. People aged 75 and older contact their general practitioner more than 16 times a year,[37] which often allows the general practitioner to detect relevant changes in and problems with the aging process on a personal level.

Osteoporosis, for example, is a condition in which these cultural and healthcare differences played a role in the panelists' discussions. For osteoporosis, earlier research resulted in evidence-based methods to identify risk for osteoporotic fractures and effective medications to reduce fractures, but as the U.S. Preventive Services Task Force showed in its review of July 2010,[38] no trials have directly evaluated screening effectiveness, harms, and intervals between screening. This lack of direct evidence leaves room for weighing and interpretation, apparently resulting in the overall finding that European guidelines contained negative advice to screen for osteoporosis, whereas the non-European guidelines recommended screening. In the present study, the panelists considered that, in The Netherlands, assessment of osteoporosis was already part of treatment in older people after fracture. In people using corticosteroids for a prolonged period, prevention and treatment of osteoporosis also form part of the therapeutic plan. This means that the high-risk groups are already assessed in the context of "normal" care. Only older people without a fracture and without use of corticosteroids are still unscreened. For this low-risk group, the panelists argued that, although screening for osteoporosis in general has not been proven to be effective, screening in this remaining low-risk group will be even less effective. Therefore, according to the panelists, there is insufficient evidence to support screening for osteoporosis, especially regarding the screening test (too many false negatives in this low-risk group; Wilson and Jungner criterion 5).

Strengths and limitations

The present study has several strengths. First, the focus on healthy aging by preventing functional decline is relatively new in studies on screening. In this study, the objective of screening older people was not primarily to prevent and postpone disease and death but rather to support the ability of older people to function as independently as possible.[18] The results of the study indicate the need for more high-quality studies to support the benefit of screening to prevent functional decline. Another strength is the multidisciplinary panel, because the composition of the panel is known to influence the outcome of the RAND/UCLA appropriateness method.[39] Most users of the RAND/UCLA method recommend using a multidisciplinary panel to better reflect the variety of specialties involved in decisions on treatment.[22] If another panel in which the composition in terms of disciplines is maintained repeats the same procedure, the results will be reproduced with a high level of agreement.[27,30,40] In the present study, the initial disagreement in the first round (23%) meant that the panel composition adequately reflected the different opinions about screening in health care. During the discussion, all panelists were engaged in a positive-critical way and were willing to change their opinion, if necessary.

One limitation of the present study is the specific Dutch context in which the RAND/UCLA appropriateness method was used; this might influence generalizability. It would be interesting if panels in other countries would replicate this study in order to compare the findings.

Another limitation is that it was not feasible to perform exhaustive systematic reviews for all 29 conditions for all 10 criteria of Wilson and Jungner. Instead, the literature on which the guidelines were based was collected, and experts were invited to complete and update these files with recent literature. This practical approach is in accordance with the RAND/UCLA appropriateness method.[22]

Clinical implications and future research

The results of the RAND/UCLA appropriateness method indicate that, according to the panelists, only screening of the general older population for insufficient physical activity, smoking status, and cardiovascular risk in specific groups is recommended to prevent functional decline. The uncertain or inappropriate rating of the remaining screening conditions does not mean that the conditions are not relevant but that there is insufficient evidence to recommend an active screening approach at the population level. For the conditions rated uncertain, mostly regarding the vulnerable older population, evidence was lacking, although based on their clinical experience, the panelists expected potential benefit from screening embedded in the regular care for this group of older people. It is important in future research to detect effective screening approaches and subsequent treatments to maintain functional status and related quality of life for this group. Then, screening and monitoring as part of regular care will support healthier aging by preventing or delaying functional decline.

and social support), GIJM Kempen, PhD, CAPHRI School for Public Health and Primary Care, Maastricht University (functional status), A Knuistingh Neven, MD, PhD, Leiden University Medical Center (sleep disorders), RM Kok, MD, PhD, Parnassia Psychiatric Institute (depression and anxiety), JAPM de Laat, PhD, Leiden University Medical Center (hearing impairment), A Lagro-Jansen, MD, PhD, Radboud University Nijmegen Medical Centre (urinary incontinence), P Lips, MD, PhD, VU University Medical Center (osteoporosis), F Verhey, MD, PhD, School for Mental Health and Neuroscience/Alzheimer Centre Limburg and Maastricht University Medical Center (cognitive impairment), LJ van Rijn, MD, PhD, VU University Medical Center (visual impairment), AHP Niggebrugge, MD, PhD, Bronovo Hospital (colorectal cancer and skin cancer), W de Ruijter, MD, PhD, Leiden University Medical Center (cardiovascular risk), YWJ Sijpkens, MD, PhD, Leiden University Medical Center (chronic kidney disease), PAGM de Smet, PharmD, PhD, Radboud University Nijmegen Medical Centre (polypharmacy), MM Verduijn, MSc, Dutch College of General Practitioners (pain) and G Visser, MA, Vilans, Centre of Expertise for long-term care (burden of the informal caregiver, smelling problems, social well-being, spare time, and speech problems). These experts received 150 Euro each as compensation for their contributions.

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Author Contributions: Drewes had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drewes, Gussekloo, van der Meer, Assendelft: Study concept and design. Drewes, Gussekloo, van der Meer, Rigter, Dekker, Goumans, Metsemakers, van Overbeek, de Rooij, Schers, Schuurmans, Sturmans, de Vries, Westendorp, Wind, Assendelft: Analysis and interpretation of data. Drewes: Drafting of the manuscript. Gussekloo, van der Meer, Rigter, Dekker, Goumans, Metsemakers, van Overbeek, de Rooij, Schers, Schuurmans, Sturmans, de Vries, Westendorp, Wind, Assendelft: Critical revision of the manuscript for important intellectual content.

Conflict of Interest: R van Overbeek is an employee of Knowledge Centre Vilans, whose guideline was used. The honorarium panelists received 1,000 Euro and the honorarium moderator received 2,000 Euro.

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Appendix

OVERVIEW OF THE RAND/UCLA APPROPRIATENESS METHOD[1]

Introduction

The RAND/UCLA Appropriateness Method was developed in the mid 1980s, as part of the RAND Corporation/University of California Los Angeles (UCLA) Health Services Utilization Study, primarily as an instrument to enable measurement of the overuse and underuse of medical and surgical procedures. In the RAND/UCLA Appropriateness Method, the concept of appropriateness refers to the relative weight of the benefits and harms of a medical or surgical intervention. An appropriate procedure is one in which the expected health benefit exceeds the expected negative consequences by a sufficiently wide margin that the procedure is worth doing.

Literature review

The first step in the procedure is to perform a literature review to synthesize the latest available scientific evidence on the condition.

For the current study, conditions were selected from three Dutch guidelines/protocols on screening and prevention,[2-4] and from English-language guidelines of five leading health care institutes in other countries (USA, Australia and Great Britain).[5-10] A condition was considered eligible to screen for, if it was recommended in one or more of these guidelines. For each condition separately, a scientist with expertise in the content of that condition was asked to comment on the guidelines and reference lists, and to add up-to-date information if available. These files, one for each condition, formed the evidence package for the panelists.

Developing the rating sheets

The second step in the procedure is to produce rating sheets in the form of a matrix which categorizes patients who might have an indication for the procedure in question.

For the current study, the patients were categorized in the rating sheets in three age groups (60-74 years, 75-84 years, and 85 years and older) and in three levels of health status (general, vital and vulnerable), which resulted in nine ratings per condition.

The expert panel

A third step in the process is to compose an expert panel. A panel of experts is identified, often based on recommendations from the relevant medical societies. The literature review and the list of conditions, together with a list of definitions are sent to the members of this panel.

For the current study, 11 experts from disciplines involved in geriatric care and screening were recruited from all eight university medical centers: general practice, clinical geriat-

rics, nursing home medicine, public health, nursing science, and an expert from Vilans, a Dutch Knowledge Centre on Ageing. One month before the meeting these panelists received the evidence packages, definitions of the key terms used for the procedure, the criteria of Wilson and Jungner[11] as background information, and the rating sheets.

The rating process

The fifth step is the rating by the panelists. For each indication, the panelists rate the appropriateness of the procedure. Rating is done on a 1-9 point scale, defined as follows: 1=extremely inappropriate, 5=uncertain or equivocal, and 9=extremely appropriate to screen. The panelists rate each of the indications twice, in a two-round 'modified Delphi' process. In the first round, the ratings are made individually at home, with no interaction among panelists. In the second round, the panelists meet for 1-2 days under the leadership of a moderator experienced in using the method. Each panelist receives a report of his/her own first-round ratings, a frequency distribution, and the median of the whole panel. The individual ratings are blinded to other group members. Every indication is discussed to identify areas of disagreement, to highlight evidence not cited in the literature reviews, and to clarify specific definitions or wording of the conditions. In addition, panelists can revise existing conditions to better fit their judgment as well as propose new conditions. After discussing each chapter of the list of indications, they re-rate each indication individually. The score of each panelist is equally weighted in the final ratings. No attempt is made to force the panel to consensus. Instead, the two-round process is designed to sort out whether discrepant ratings are due to real clinical disagreement over the use of the procedure ('real' disagreement) or fatigue or misunderstanding ('artifactual' disagreement). This rating procedure combined the best available scientific evidence with the collective judgment of experts.

In the present study, the expert panel was instructed to assess the contribution of screening for each specific condition to the prevention or postponement of functional decline. The expert panel was asked to rate each condition on a 1-9 point scale (1=extremely inappropriate, 5=uncertain or equivocal, and 9=extremely appropriate to screen) for each of the three age groups (60-74 years, 75-84 years and 85 years and older) and for each of the three levels of health status (general, vital and vulnerable). At the start of the face-to-face meeting, each panelist received a report of his/her own first-round ratings, a frequency distribution of the ratings of all panelists, and the median of the whole panel (Figure 1). During the meeting, each condition was discussed, especially disagreements, and re-rated thereafter. The expert panel followed the criteria of Wilson and Jungner for each condition: the panelists investigated whether sufficient evidence was present to fulfill the criteria for a specific condition and they took their expert opinion about a possible benefit into account.

Classifying appropriateness

Finally, each indication is classified as 'appropriate', 'uncertain' or 'inappropriate' for the procedure under review in accordance with the panelists' median score and the level of disagreement among the panelists. Indications with median scores in the 1-3 range are classified inappropriate, those in the 4-6 range as uncertain, and those in the 7-9 range as appropriate. However, all indications rated 'with disagreement', whatever the median, are classified as uncertain. 'Disagreement' basically means a lack of consensus, either because there is polarization of the group or because judgments are spread over the entire 1-9 rating scale. Various alternative definitions for disagreement have been used throughout the history of the RAND/UCLA appropriateness method.

In the present study, a condition was considered to be rated 'with disagreement' when at least three panelists rated in the 1-3 range, and at least three panelists rated in the 7-9 range.[12]
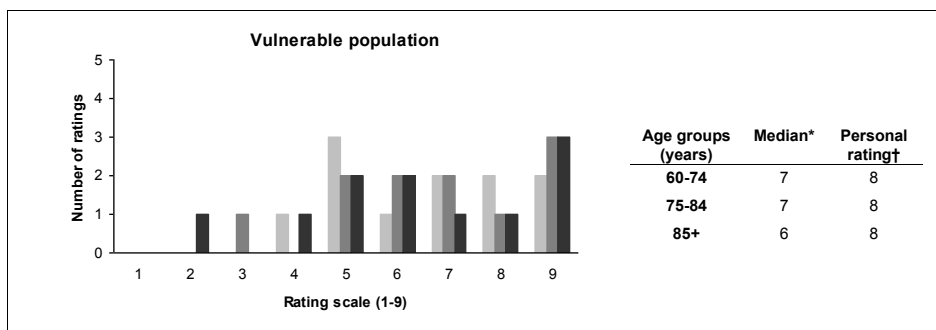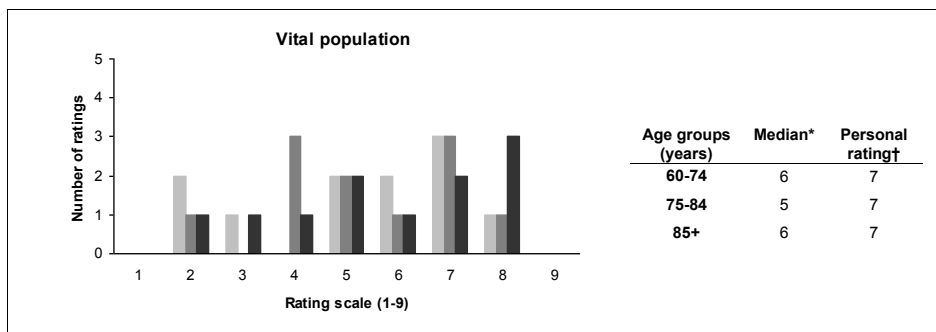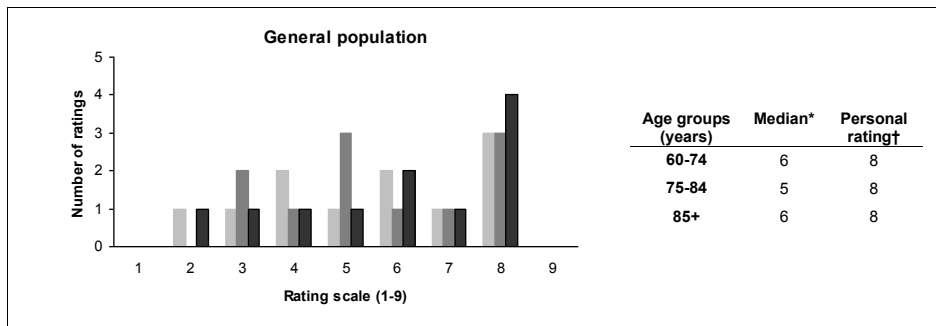
Figure 1. Example of a personal report of the first rating round for physical activity

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Chapter 6

Prognostic value of cardiovascular disease status: the Leiden 85-plus Study

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ABSTRACT

This study aimed to explore the prognosis of very old people depending on their cardiovascular disease (CVD) history. This observational prospective cohort study included 570 participants aged 85 years from the general population with 5-year follow-up for morbidity, functional status, and mortality. At baseline, participants were assigned to three groups: no CVD history, "minor" CVD (angina pectoris, transient ischemic attack, intermittent claudication, and/or heart failure), or "major" CVD (myocardial infarction [MI], stroke, and/or arterial surgery). Follow-up data were collected on MI, stroke, functional status, and cause-specific mortality. The composite endpoint included cardiovascular events (MI or stroke) and cardiovascular mortality. At baseline, 270 (47.4%) participants had no CVD history, 128 (22.4%) had minor CVD, and 172 (30.2%) had major CVD. Compared to the no CVD history group, the risk of the composite endpoint increased from 1.6 (95% confidence interval [CI], 1.1–2.4) for the minor CVD group to 2.7 (95% CI, 2.0–3.9) for the major CVD group. Similar trends were observed for cardiovascular and all-cause mortality risks. In a direct comparison, the major CVD group had a nearly doubled risk of the composite endpoint (hazard ratio, 1.8; 95% CI, 1.2–2.7), compared to the minor CVD group. Both minor and major CVD were associated with an accelerated decline in cognitive function and accelerated increase of disability score (all $p < 0.05$), albeit most pronounced in participants with major CVD. CVD disease status in very old age is still of important prognostic value: a history of major CVD (mainly MI or stroke) leads to a nearly doubled risk of poor outcome, including cardiovascular events, functional decline, and mortality, compared with a history of minor CVD.

INTRODUCTION

Cardiovascular disease (CVD) is characterized by a high prevalence and incidence up to the highest age groups. Moreover, cardiovascular morbidity is an important cause of disability and, from middle age onwards, CVD is the leading cause of death.[1,2] Therefore, prevention of cardiovascular events has high priority and risk prediction models have been developed.

In daily practice, populations are usually dichotomized into people with known athero-thrombotic CVD, such as coronary heart disease, stroke/transient ischemic attack (TIA), and peripheral arterial disease, and people without those manifest conditions, but possibly with risk factors for CVD, such as hypertension, hypercholesterolemia, diabetes, or smoking.[3-6] Persons without manifest CVD theoretically qualify for the so-called primary prevention, be it on a population scale or on a more personal level when their calculated CVD risk exceeds predefined thresholds.[5,7] Persons with prior CVD are known to have a high risk of recurrent CVD[8-11] and should, therefore, receive optimal "secondary prevention", including lifestyle advice and preventive medication. Despite evidence of its value also in old age, elderly people do not receive optimal preventive treatment even after major events.[12-14] At very old age, drug interactions, intoxications, and adverse effects can have serious impact on the quality of life.[15] Therefore, further risk differentiation within those with prior CVD might help clinicians to select those at the highest risk of recurrent events. In younger age groups, it is already known that patients with prior CVD are at the highest risk of a recurrent cardiovascular event.[8] Within patients with prior CVD, a recent study showed that a history of ischemic events leads to a greater risk of future events than a history of stable coronary, cerebrovascular, or peripheral artery disease.[16] At present, it is unknown whether these findings can also be applied to patients aged 85 and over.

We hypothesized that subgroups with different risks of recurrent CVD might also be observed within the population of the oldest old. A history of myocardial infarction (MI) or stroke might have a different prognosis than a history of relatively "minor" CVD such as stable angina or claudication, TIA, or milder cases of heart failure. This may have clinical consequences for the format and intensity of secondary prevention in these groups of older people.

We investigated whether differences in prognosis exist between very old people with various levels of prevalent CVD, compared to those with no manifest CVD. Since in older populations the outcomes "morbidity" and "functional status" become even more

important than mortality, we studied the prognosis not only regarding (cause-specific) mortality, but also with respect to recurrent CVD morbidity and functional status.

METHODS

Study population

The Leiden 85-plus Study is a prospective population-based study in 85-year-old inhabitants of the city of Leiden, The Netherlands. The study design and characteristics of the cohort have previously been described in detail.[17,18] In brief, between September 1997 and September 1999, 705 people from the 1912–1914 birth cohorts living in the city of Leiden who reached the age of 85 years were eligible to participate. No exclusion criteria were used. From the 705 people who were eligible at age 85, 92 refused participation and 14 died before enrolment. A total of 599 (87%) people gave informed consent and were enrolled. At baseline and yearly up to the age of 90 years, participants were visited at their place of residence to obtain extensive data on health, functioning, and well-being. In addition, a medical history was obtained from the participant's primary care physician. For all participants, classic cardiovascular risk factors were determined. The Medical Ethics Committee of the Leiden University Medical Centre approved the study.

Prevalence of CVD at age 85 years

For each participant, the primary care physician was interviewed about the history of CVD using a standardized questionnaire, which included questions on present and past cardiovascular pathologies, including MI, stroke, surgery for arterial disease (aorta, carotid, coronary, or peripheral arteries), angina pectoris, TIA, intermittent claudication, and heart failure. An ECG was recorded. The presence of MI on the ECG was defined as the presence of Minnesota Code 1-1 or 1-2 (excluding 1-2-8). Participants were assigned to three different groups according to their CVD status: a group with no known history of CVD (reference group), a group with a history of "minor" CVD, and a group with a history of "major" CVD. Minor CVD was considered present if the primary care physician had recorded a history of angina pectoris, TIA, intermittent claudication, and/or heart failure. Major CVD was defined as a history of MI (including MI on baseline ECG), stroke, or surgery for arterial disease (aorta, carotid, coronary, or peripheral arteries). These criteria for minor and major CVD were based on literature in younger age groups.[14,19]

Clinical endpoints

(Non)fatal myocardial infarction
Up to 90 years of age, all incident fatal and nonfatal MIs were annually registered using data from the primary care physician, ECGs, and death registration forms. Incident MI

on the ECG was defined as the appearance of Minnesota Code 1-1 or 1-2 or Minnesota Code 1-3 in combination with the first appearance of Minnesota Code 5-x in the same myocardial area.[20] A fatal incident MI was categorized by cause of death codes I21–I23 (International Classification of Diseases [ICD]-10).

(Non)fatal stroke
Information on incident stroke was collected annually from the primary care physician up to 90 years of age. A fatal incident stroke was categorized by cause of death codes I61–I69 (ICD-10).

Incident cardiovascular events or cardiovascular mortality
The composite endpoint "incident cardiovascular events or cardiovascular mortality" was defined as fatal and nonfatal MI, fatal and nonfatal stroke, or other cardiovascular mortality.

Mortality
All participants were followed up for mortality until the age of 95 years. Dates and causes of death were obtained from civic and national registries. Causes of death were divided into cardiovascular causes (ICD-10 codes I00–I99) and noncardiovascular causes (all other ICD-10 codes). Assignment of cause of death was done blinded for baseline and follow-up study data.

Functional status
Up to 90 years of age, participants were annually visited by a research nurse at their place of residence. Cognitive function was assessed by the Mini-Mental State Examination (MMSE) with scores ranging from 0 to 30 points (optimal).[21] Disability was assessed using the Activities of Daily Living (ADL) items from the Groningen Activity Restriction Scale with scores ranging from 9 (optimal) to 36 points.[22] In those with MMSE scores above 18, Cantril's Ladder of Life with a score from 1 to 10 (optimal) points was used as a measure of general well-being[23] and the 15-item Geriatric Depression Scale (GDS) with scores ranging from 0 (optimal) to 15 points was used to screen for depressive symptoms.[24]

Statistical analysis

Differences in baseline characteristics between the groups according to CVD status were analyzed with the chi-square test for categorical variables and the Jonckheere-Terpstra test for continuous variables. Time-to-event curves were constructed with the Kaplan–Meier method and compared using a log-rank test. If no exact time to event was available, the time to event was calculated as halfway that particular year. Mortality and morbidity

hazard ratios (HR) and corresponding 95% confidence intervals (CIs) were calculated in a Cox proportional hazards model adjusted for sex. The same HRs were calculated in a model with additional adjustments for the use of antihypertensive medication, income, and level of education. Incidence rate was calculated using the timetable method as number of incidents per 1,000 person-years at risk with corresponding 95% CIs. Differences in cognitive function (MMSE), changes in disability (ADL), general well-being (Cantril), and depressive symptoms (GDS) were estimated using linear mixed models adjusted for sex and are presented as (predicted) means with standard errors. As a first sensitivity analysis, the stratification in groups according to CVD status was repeated at the age of 90 years, with updated information about incidence of cardiovascular events from 85 to 90 years of age. A second sensitivity analysis was done with risk groups according to site of CVD: a group with a history of cardiac CVD (angina pectoris and/or MI), a group with a history of cerebrovascular CVD (TIA and/or stroke), a group with a history of peripheral CVD (intermittent claudication and/or surgery for noncoronary arterial disease), and a group with a history of CVD at multiple sites. Data analysis was performed using SPSS 17.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Baseline characteristics

For 570 of the 599 participants, all baseline measurements were available. At 85 years of age, 270 (47.4%) participants had no history of CVD, 128 (22.4%) participants had minor CVD, and 172 (30.2%) participants had major CVD (Table 1). Participants with major CVD were more often men (47 versus 27% for minor CVD and 28% for no CVD, p_{trend} <0.001) and more often institutionalized (23 versus 18% for minor CVD and 15% for no CVD, p_{trend}=0.048). They had higher scores of disability (p_{trend}=0.009) and their MMSE scores were the lowest (p_{trend} <0.001). Only 36% of the participants with minor CVD and 51% of the participants with major CVD used aspirin or oral anticoagulants. Median systolic blood pressure was 154 mmHg (interquartile range [IQR], 143–166), median total cholesterol was 5.7 mmol/L (IQR, 4.9–6.4). Participants with major CVD had lower HDL cholesterol levels (p_{trend} <0.001). Use of statins was minimal: no more than 1% of all participants used lipid-lowering drugs. From all participants with heart failure (n=74), more than half (n=38 [51%]) also had a history of major CVD.

At 90 years of age, 303 (53%) participants were still alive. Follow-up for mortality was complete, and for 296 participants, we completed all clinical measurements at 90 years.

Table 1. Baseline characteristics of participants from the Leiden 85-plus Study (n=570), depending on cardiovascular history.

	Total	CVD history			p for trend [a]
		None	**Minor**	**Major**	
	570 (100)	**270 (47.4)**	**128 (22.4)**	**172 (30.2)**	
Sociodemographic characteristics					
Women	379 (67)	195 (72)	93 (73)	91 (53)	<0.001
Net monthly income >750€	276 (49)	147 (55)	52 (41)	77 (45)	0.058
Post primary school education	197 (35)	104 (39)	41 (32)	52 (31)	0.091
Noninstitutionalized living	467 (82)	229 (85)	105 (82)	133 (77)	0.048
Functional status					
Cognitive function (MMSE)	26 (22-28)	27 (24-29)	26 (23-28)	25 (19-28)	<0.001
ADL disability	10 (9-15)	10 (9-13)	10 (9-15)	10 (9-16)	0.009
Subjective well-being (Cantril) [b]	8 (7-9)	8 (6-9)	8 (7-8)	8 (7-9)	0.177
Depressive symptoms (GDS) [b]	2 (1-3)	2 (1-3)	2 (1-4)	2 (1-3)	0.636
Cardiovascular characteristics					
Classic risk factors					
Hypertension [c]	325 (58)	134 (50)	87 (68)	104 (64)	0.003
RR systolic, mmHg	154 (143-166)	155 (144-166)	154 (142-168)	153 (141-166)	0.332
Hypercholesterolemia [d]	123 (22)	59 (22)	30 (24)	34 (22)	0.928
Total cholesterol, mmol/L	5.7 (4.9-6.4)	5.7 (5.0-6.4)	5.8 (4.9-6.4)	5.6 (4.8-6.3)	0.320
HDL cholesterol, mmol/L	1.3 (1.0-1.6)	1.3 (1.1-1.6)	1.3 (1.0-1.5)	1.1 (0.9-1.4)	<0.001
BMI, kg/m^2	27 (24-30)	27 (25-30)	27 (24-31)	26 (24-29)	0.096
Diabetes [e]	89 (16)	38 (14)	19 (15)	32 (20)	0.151
Smoking [f]	267 (49)	122 (46)	54 (42)	91 (58)	0.029
Medication use					
Blood pressure lowering drugs [g]	316 (57)	111 (42)	92 (72)	113 (71)	<0.001
Anticoagulants/aspirin	162 (28)	28 (10)	46 (36)	88 (51)	<0.001
Lipid-lowering drugs	6 (1)	1 (0.4)	2 (1.6)	3 (1.7)	0.15
Cardiovascular history					
Angina	109 (19)	0	60 (48)	49 (29)	
Transient ischemic attack	75 (13)	0	40 (31)	35 (21)	
Intermittent claudication	37 (7)	0	12 (10)	25 (15)	
Heart failure	74 (13)	0	36 (28)	38 (22)	
Myocardial infarction	99 (17)	0	0	99 (58)	
Stroke	61 (11)	0	0	61 (36)	
Surgery for arterial disease [h]	42 (7)	0	0	42 (25)	

Data presented as n (%) for categorical variables, and median (IQR) for continuous variables.
CVD=cardiovascular disease; No CVD=participants with no history of CVD; Minor CVD=participants with a history of angina, transient ischemic attack, intermittent claudication or heart failure; Major CVD=participants with a history of myocardial infarction, stroke or surgery for arterial disease ; MMSE=Mini-Mental State Examination (range 0-30); ADL=basic activities of daily living (range 9-36); Cantril=Cantril's ladder of life (range 0-10); GDS=Geriatric Depression Scale (range 0-15)
[a] Chi-square test for categorical variables and Jonckheere-Terpstra for continuous variables; [b] assessed only in participants with MMSE >18; [c] RR ≥160 systolic at baseline or a history of hypertension; [d] total cholesterol ≥6.5 at baseline or statin use; [e] history of diabetes, antidiabetic medication use or non-fasting glucose ≥11 mmol/L; [f] current or past smoker; [g] use of ß-blockers, ACE inhibitors, diuretics or calciumchannel blockers as reported by the participants pharmacists; [h] aorta, carotid, coronary or peripheral arteries

Morbidity and mortality

During 5 years of follow-up, 181 (32%) participants reached the composite endpoint, including 76 (42%) fatal and nonfatal MI, 76 (42%) fatal and nonfatal strokes, and 29 (16%) additional cardiovascular deaths. Figure 1 shows the Kaplan–Meier curves for the three groups for the composite endpoint "incident cardiovascular events or cardiovascular mortality" (left panel) and all-cause mortality (right panel). Overall, during these 5 years, 267 (47%) participants died; of which, 106 (40%) died from cardiovascular causes. The incidence rate for "incident cardiovascular events or cardiovascular mortality" increased from 56 (95% CI, 44–72) per 1,000 person-years at risk in the group with no CVD to 88 (95% CI, 65–118) in the group with minor CVD and to 164 (95% CI, 144–199) in the group with major CVD (Table 2). The risks for a fatal or nonfatal MI, a fatal or nonfatal stroke, and the composite endpoint increased from 1.7 (95% CI, 0.9–3.1), 1.7 (95% CI, 0.9–3.2), and 1.6 (95% CI, 1.1–2.4), respectively, in participants with minor CVD to 2.6 (95% CI, 1.6–4.5), 3.4 (95% CI, 2.0–5.8), and 2.7 (95% CI, 2.0–3.9), respectively, in those with major CVD. In a direct comparison of the group with major CVD with the group with minor CVD, the risk of the composite endpoint was nearly doubled in the major CVD group (HR, 1.8; 95% CI, 1.2–2.7).

For cardiovascular mortality, the risks increased from 2.0 (95% CI, 1.1–3.4) in the minor CVD group to 3.7 (95% CI, 2.3–5.8) in the major CVD group (p_{trend} <0.001). For all-cause mortality, the risks rose from 1.7 (95% CI, 1.2–2.3) in the minor group to 2.3 (95% CI, 1.7–3.1) in the major group (p_{trend} <0.001). After adjustment for the use of antihypertensive medication, income, and level of education, all these estimates remained roughly similar (data not shown). When we analyzed the HRs with 10-year follow-up, we found similar risks for cardiovascular and all-cause mortality: HR, 1.5 (95% CI, 0.99–2.2) and 1.4 (95% CI, 1.1–1.8), respectively, for minor CVD and HR, 2.6 (95% CI, 1.9–3.7) and 2.0 (95% CI, 1.6–2.5), respectively, for major CVD.

Functional status

At baseline, there were no differences in functional status between participants with minor CVD and those with no CVD (Table 3; Fig. 2). But the MMSE score was lower (−2.8 points, p <0.001) and ADL disability score was higher (2.6 points, p=0.003) in participants with major CVD. Compared to participants with no CVD, participants with minor CVD had an additional annual decrease in MMSE score of −0.19 points (p=0.023) and increase in ADL disability score of 0.25 points (p=0.042) over time. Participants with major CVD had an additional annual decrease in MMSE score (−0.24 points, p=0.005) and increase in ADL disability score (0.61 points, p <0.001). Compared to participants with minor CVD, participants with major CVD had an additional annual increase in ADL disability score of 0.36 points (p=0.023). All other changes in functional status over time were not significant.
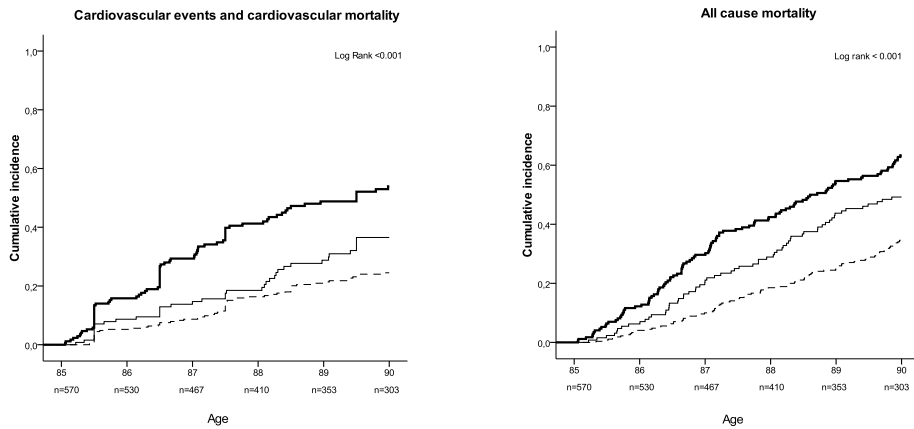
Figure 1. History of cardiovascular disease (CVD) and 5-year incidence of the composite endpoint 'myocardial infarction, stroke and cardiovascular mortality' (*left panel*), as well as incidence of all-cause mortality (*right panel*) for three groups with no history of CVD, a history of minor CVD and a history of major CVD, respectively. *Thick solid line* major CVD, *thin solid line* minor CVDE, *dashed line* no CVD

Sensitivity analyses

At 90 years of age, participants were recategorized with the updated clinical information from 85 to 90 years of age. Of the participants with complete data at 90 years of age (n=296), 119 (40%) had no history of CVD, 93 (31%) had minor CVD, and 84 (28%) had major CVD. In participants with minor CVD, the 5-year risk for cardiovascular mortality (up to 95 years of age) was not significantly increased (1.1; 95% CI, 0.6–1.9), but participants with major CVD had a more than twofold increased risk (HR, 2.1; 95% CI, 1.2–3.7). For all-cause mortality, the HRs were 1.1 (95% CI, 0.79–1.5) and 2.1 (95% CI, 1.5–3.0), respectively.

The second sensitivity analysis was done with different groups according to the site of their CVD. There were 25 participants (4.4%) with peripheral CVD, 73 (12.8%) with cerebrovascular CVD, 109 (19.1%) with cardiac CVD, and 66 (11.6%) with CVD on more than one site (Table 4). HRs were all calculated with the group with no CVD as reference group. The HR for fatal or nonfatal stroke was as high as 3.9 (95% CI, 2.2–6.9) for those with previous TIA or stroke, and the HR for fatal or nonfatal MI was particularly high (3.4; 95% CI, 1.9–6.4) in the group with CVD on multiple sites. The HR for cardiovascular mortality was highest in participants with peripheral CVD (3.8; 95% CI, 1.7–8.5). In contrast with this high risk of cardiovascular mortality, the HRs for fatal or nonfatal MI and fatal or nonfatal stroke in participants with peripheral CVD were low, nearly equal to the group with no CVD (1.0; 95% CI, 0.23–4.3 and 1.4; 95% CI, 0.32–5.8, respectively). Except for the above-mentioned HRs, the groups did not differ materially.

Table 2. Five-year hazard ratios and absolute risks of cardiovascular morbidity and mortality, depending on cardiovascular history, adjusted for sex (n=570).

	CVD history				
	None (n=270)	**Minor (n=128)**	**Major (n=172)**	**p for trend**	**HR major vs. minor**
Morbidity and mortality					
Fatal and non-fatal MI					
HR	1	1.7 (0.9-3.1)	2.6 (1.6-4.5)	0.001	1.8 (0.97-3.2)
No. of events	25 (9.3)	17 (13.3)	34 (19.8)		
Incidence rate	23 (15-33)	37 (23-58)	65 (47-90)		
Fatal and non-fatal stroke					
HR	1	1.7 (0.9-3.2)	3.4 (2.0-5.8)	<0.001	2.0 (1.1-3.6)
No. of events	23 (8.5)	16 (12.5)	37 (21.5)		
Incidence rate	20 (14-30)	35 (21-56)	69 (51-94)		
CV events or CV mortality [a]					
HR	1	1.6 (1.1-2.4)	2.7 (2.0-3.9)	<0.001	1.8 (1.2-2.7)
No. of events	61 (22.6)	39 (30.5)	81 (47.1)		
incidence rate	56 (44-72)	88 (65-118)	164 (144-199)		
Mortality					
Cardiovascular					
HR	1	2.0 (1.1-3.4)	3.7 (2.3-5.8)	<0.001	1.9 (1.2-3.1)
No. of events	29 (10.7)	23 (18.0)	54 (31.4)		
Incidence rate	25 (18-36)	48 (32-71)	95 (74-122)		
Non cardiovascular					
HR	1	1.5 (1.03-2.3)	1.7 (1.2-2.5)	0.001	1.1 (0.7-1.7)
No. of events	66 (24.4)	40 (31.3)	55 (32.0)		
Incidence rate	57 (54-72)	83 (62-111)	97 (75-124)		
All-cause					
HR	1	1.7 (1.2-2.3)	2.3 (1.7-3.1)	<0.001	1.4 (1.02-1.9)
No. of events	95 (35.2)	63 (49.2)	109 (63.4)		
Incidence rate	82 (68-100)	131 (104-164)	193 (162-227)		

Data presented as hazard ratios (HR) with corresponding 95% confidence intervals, absolute numbers of events (%), and incidence rates as number of incidents per 1000 person years at risk with corresponding 95% confidence intervals. CVD=cardiovascular disease; No CVD=participants with no history of cardiovascular disease (CVD); Minor CVD=participants with a history of angina, transient ischemic attack, intermittent claudication or heart failure; Major CVD=participants with a history of myocardial infarction, stroke or surgery for arterial disease (aorta, carotid, coronary, or peripheral arteries) [a] composite endpoint: fatal and non-fatal myocardial infarction, fatal and non-fatal stroke and cardiovascular mortality

Table 3. Association between history of cardiovascular disease at age 85 years and (changes in) functional status from age 85 through 90 years (n=570).

| | Cross-sectional effect[a] | | | | Annual effect reference group | | Additional annual effect[a] | | | |
| | Minor CVD | | Major CVD | | | | Minor CVD | | Major CVD | |
	B (SE)	p value	B (SE)	p value	B (SE)	p value	B (SE)	p value	B (SE)	p value
MMSE	-0.65 (0.69)	0.35	-2.8 (0.69)	<0.001	-0.67 (.045)	<0.001	-0.19 (0.084)	0.023	-0.24 (0.085)	0.005
ADL disability	0.58 (0.71)	0.41	2.6 (0.72)	0.003	1.1 (0.066)	<0.001	0.25 (0.12)	0.042	0.61 (0.13)	<0.001
Cantril scale of well-being	-0.021 (0.17)	0.90	0.24 (0.17)	0.15	-0.20 (.021)	<0.001	0.039 (0.041)	0.35	-0.045 (0.043)	0.29
Geriatric depression scale	0.060 (0.31)	0.85	0.033 (0.31)	0.92	0.30 (.035)	<0.001	-0.023 (0.069)	0.74	0.030 (0.070)	0.66

Associations were assessed by linear mixed models adjusted for sex; Scale: MMSE 0-30 points, ADL disability 9-36 points, Cantril 0-10 points, Geriatric Depression scale of depressive symptoms 0-15 points

CVD cardiovascular disease.

[a] reference group: group with no CVD at baseline

Table 4. Five-year hazard ratios for cardiovascular morbidity and mortality for participants, depending on specific site of cardiovascular history adjusted for sex (n=570).

	CVD history				
	None (n=297)	Cardiac (n=109)	Cerebrovascular (n=73)	Peripheral (n=25)	Multiple sites (n=66)
Morbidity					
Fatal and nonfatal MI	1	2.0 (1.1-3.7)	1.9 (0.96-3.9)	1.0 (0.23-4.3)	3.4 (1.9-6.4)
Fatal and nonfatal stroke	1	2.3 (1.3-4.2)	3.9 (2.2-6.9)	1.4 (0.32-5.8)	1.6 (0.68-3.7)
CV events or CV mortality [a]	1	2.0 (1.4-3.0)	2.3 (1.5-3.5)	1.9 (0.93-3.8)	2.5 (1.6-3.9)
Mortality					
Cardiovascular	1	2.8 (1.7-4.6)	3.0 (1.7-5.3)	3.8 (1.7-8.5)	3.1 (1.7-5.5)
Noncardiovascular	1	1.4 (0.90-2.1)	1.5 (0.95-2.4)	1.6 (0.76-3.3)	1.6 (1.0-2.6)
All-cause	1	1.8 (1.3-2.5)	2.0 (1.4-2.8)	2.2 (1.3-3.8)	2.0 (1.4-3.0)

Data presented as hazard ratios (HR) with corresponding 95% CIs

CVD cardiovascular disease, *Cardiac* angina or MI; *Cerebrovascular* TIA or stroke; *Peripheral* claudication or operation for non-coronary arterial disease; *Multiple sites* CVD on more than one of cardiac, cerebrovascular or peripheral sites

[a] Composite endpoint: fatal and nonfatal MI, fatal and nonfatal stroke and cardiovascular mortality

DISCUSSION

In this cohort of oldest old from the general population, participants with a history of major CVD had a markedly increased risk of recurrent MI, stroke, and functional decline, as well as cardiovascular and all-cause mortality. Patients with a history of minor CVD had a relatively better prognosis: in nonagenarians, a history of minor CVD was not associated with mortality anymore. This implies that, within the group of very old patients who are eligible for secondary prevention, different risk groups can now be identified on the basis of clinical information only. Since the prevention of morbidity and subsequent loss of independency is increasingly important in the aging Western societies, cardiovascular prevention remains essential up to the highest age groups. Our findings underscore the importance of adequate secondary preventive measures in those with a history of major cardiovascular events, since these measures have been shown to be effective up to high ages.[25-33] On the other hand, our results suggest that the potential yield of secondary preventive measures in the oldest old might be less in older persons with a history of minor CVD.

Our study is the first to analyze prognosis based on a history of "minor" and "major" CVD in the general population of the oldest old. This distinction between minor and major CVD is based on the difference in risk of cardiovascular events and mortality after angina or TIA compared with the risk after an MI or stroke, which has been described in younger patients.[19,34,35] Our study now also showed a significant difference in cardio-

vascular morbidity and mortality between groups with a history of minor and major CVD in participants aged 85 years and over. Most other studies, performed in younger age groups, have evaluated risks after an event in a specific cardiovascular bed (cardiac, cerebral, or peripheral)[34,36-38] or observed differences in risk between one or multiple CVD sites.[10,36,37,39] The high risk of recurrent stroke in the group with a history of TIA or stroke that we observed is in line with previous studies.[10,34,39,40]

In keeping with earlier reports, in the present study, the risk of cardiovascular mortality was remarkably high in participants with peripheral artery disease, whereas cardiovas-
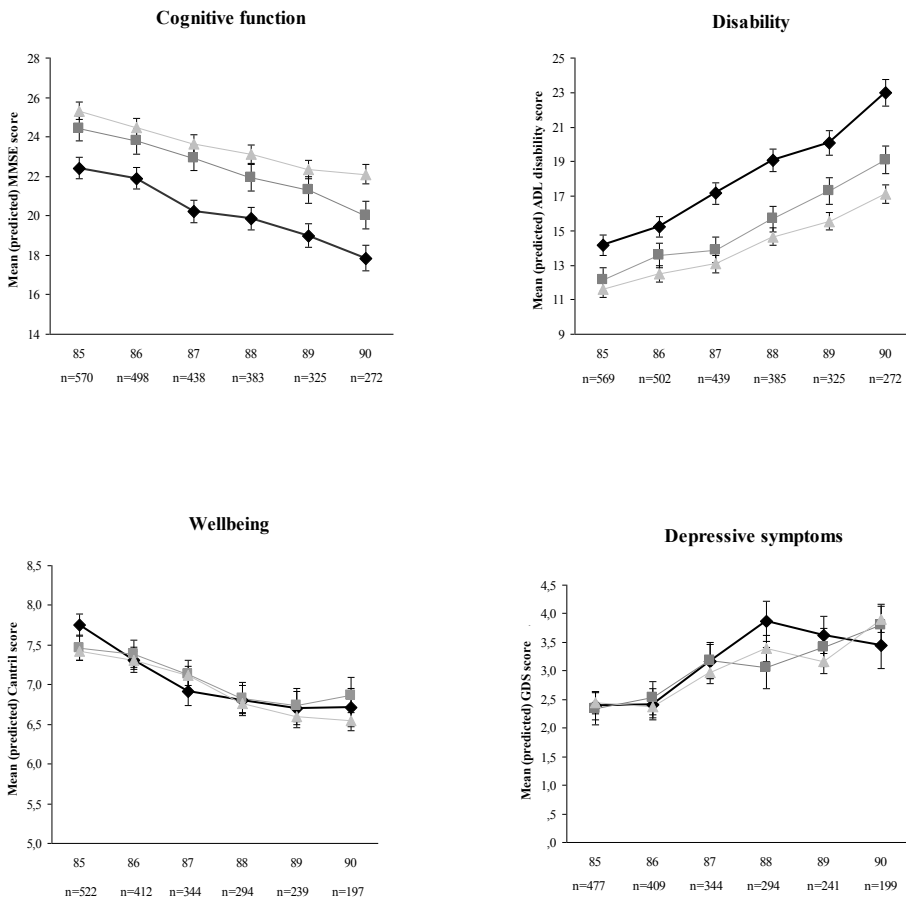
Figure 2. Changes in cognitive function, disability, subjective well-being, and depressive symptoms over time as estimated from linear mixed models adjusted for sex. Data are presented as the means with standard errors. *Triangles* reference group with no history of CVD, *squares* minor CVD, *diamonds* major CVD

cular morbidity risk in this group was relatively low.[10,34,39,40] In contrast with younger age groups, mortality risks in our study were not higher in participants with multiple-site CVD.[10,36,37,39] In very old age, it seems that major CVD, rather than multiple CVD, is of prognostic value.

Previous studies have revealed a significant decline in physical functioning after stroke and MI in 70-year-olds[41,42] and a negative impact on neurocognitive function.[42-44] Our study confirmed these data in the very old.

Our study has several strengths. First, our results can be easily applied in day to day medical practice. The current electronic medical records provide clinicians a rapid overview of the cardiovascular history without any extra costs or effort. Secondly, our population-based study had a high participation rate (87%) and no exclusion criteria, both allowing our conclusions to be generalized to the oldest old in the general population. Finally, we studied multiple relevant outcomes for an ageing population: mortality, morbidity, and functional status. A limitation might be that CVD history was based on the diagnosis of the primary care physicians, using variable diagnostic standards. However, this reflects clinical reality in primary care and previous research has shown the accuracy of data recorded in general practice to be very high.[45] In view of the fact that this study was the first to discriminate major and minor CVD in very old age, we recommend that this analysis be repeated in another cohort.

Evidence that medication for secondary cardiovascular prevention is recommendable up to the highest age groups is increasing.[25-33,46] In this cohort, the use of secondary preventive medication was far from optimal, leaving room for improvement. From our results, it can be derived that distinct groups are discernible within those who should receive secondary prevention. This is an important finding, since at very old age, polypharmacy,[15,47] treatment adherence,[13] and the delicate balance between benefit and harm[13,47,48] raise a challenge for clinicians in day to day practice.[49,50] The results of our study may help them to make appropriate treatment decisions, taking all relevant prognostic information into account.

In conclusion, in very old age, the CVD history is an easy tool for clinicians to identify patients who are at high risk for new cardiovascular events, functional decline, and cardiovascular mortality, as well as all-cause mortality. A history of major CVD nearly doubles the risk of a recurrent cardiovascular event or cardiovascular mortality compared with a history of minor CVD. Our results encourage both physicians and 85-year-olds with a history of major CVD to maximize their cardiovascular preventive efforts. However, when adverse effects or harmful interactions arise in a very old patient with minor CVD, the

balance between benefit and harm could change and strict continuation of preventive medication might be reconsidered.

ACKNOWLEDGMENTS

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Chapter 7

Homocysteine levels and treatment effect in the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER)

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ABSTRACT

Objectives

To assess the effect of preventive pravastatin treatment on coronary heart disease (CHD) morbidity and mortality in older persons at risk for cardiovascular disease, stratified for plasma levels of homocysteine.

Design

A post-hoc subanalysis in the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER), started 1997, which is a double-blinded randomized placebo-controlled trial with a mean follow-up of 3.2 years.

Setting

Primary care setting in two of the three PROSPER study sites (Netherlands and Scotland).

Participants

Individuals (n=3522, aged 70-82 years, 1765 men) with a history of or risk factors for cardiovascular disease, were ranked in three groups depending on baseline homocysteine, sex and study site.

Intervention

40 mg pravastatin versus placebo.

Measurements

Fatal and nonfatal CHD and mortality.

Results

In the placebo group, participants with high homocysteine (n=588) had a 1.8 higher risk (95% CI 1.2–2.5, p=0.001) of fatal and nonfatal CHD compared to low homocysteine (n=597). The absolute risk reduction in fatal and nonfatal CHD with pravastatin treatment was 1.6% (95% CI -1.6–4.7) in the low homocysteine group vs. 6.7% (95% CI 2.7–10.7) in the high homocysteine group (difference 5.2%, 95% CI 0.11–10.3, p=0.046). Therefore, the number needed to treat (NNT) with pravastatin for 3.2 years for benefit related to fatal and nonfatal CHD events was 14.8 (95% CI 9.3–36.6) for high homocysteine compared to 64.5 (95% CI 21.4–∞) for low homocysteine.

Conclusion

In older persons at risk for cardiovascular disease, those with high homocysteine are at highest risk for fatal and nonfatal CHD. With pravastatin treatment, this group has the highest absolute risk reduction and the lowest NNT to prevent fatal and nonfatal CHD.

INTRODUCTION

The aim of cardiovascular risk management is to reduce the incidence of cardiovascular events in a high-risk population. To select those with high cardiovascular risk, clinical cardiovascular risk scores, such as the Framingham Risk Score[1] and the Systematic Coronary Risk Evaluation (SCORE)[2], are used worldwide. However, their accuracy to predict risk on cardiovascular outcomes declines with advancing age.[3-6] Because the prevalence and incidence of cardiovascular disease increases exponentially with age,[7-9] it is suggested to offer preventive treatment to everyone over a specified age without measuring other risk factors.[10] Others, however, emphasize the need for risk stratification in old age.[11;12] Recently, the Leiden 85-plus Study (and others) showed that homocysteine is predictive of cardiovascular events in old age.[13-18]

Since, according to Wilson and Jungner, risk predictors are only clinically meaningful when effective preventive treatment is available,[19] we need to establish which treatment possibilities exist (and are appropriate) for older persons with high homocysteine to lower their cardiovascular risk. Large randomized controlled trials (RCTs) and meta-analyses show that lowering plasma homocysteine by treatment with folate has no beneficial effect on the incidence of cardiovascular events.[16;20;21] The PROspective Study of Pravastatin in the Elderly at Risk (PROSPER)[22] has shown that pravastatin lowers the risk of coronary heart disease (CHD) in older people in general, but not the risk for fatal or non-fatal strokes. We questioned whether older persons with high homocysteine levels would benefit more from this conventional preventive treatment, also compared to those with lower levels. Therefore, we performed a post-hoc subanalysis in PROSPER (a large double-blinded randomized placebo-controlled trial) to assess the effect of pravastatin on CHD risk and mortality in older persons, stratified for plasma levels of homocysteine.

METHODS

Study design
The protocol of PROSPER has been published elsewhere.[23] Briefly, in 1997-1999 a total of 5804 individuals were enrolled in Scotland (n=2520), Ireland (n=2184) and the Netherlands (n=1100). Men and women aged 70-82 years were recruited, with either pre-existing vascular disease (coronary, cerebral, or peripheral) or an increased risk of such disease because of smoking, hypertension or diabetes. Their plasma total cholesterol was required to be 154-347 mg/dl (4.0-9.0 mmol/L) and their triglyceride concentrations ≤531 mg/dl (≤6.0 mmol/L). Individuals with congestive heart failure (New York Heart

Association functional class III and IV) or poor cognitive function (Mini-Mental State Examination (MMSE) score <24 points) were excluded. Participants were randomized either to a group receiving 40 mg pravastatin a day or to a control group receiving a placebo, and were followed (on average) for 3.2 years. Throughout the study, all study personnel was unaware of the allocated study medication status of the patients. The institutional ethics review boards of all centers approved the protocol, and all participants gave written informed consent.

Determination of homocysteine

After blood drawing, blood samples were kept at room temperature until they were processed in the laboratory to be stored in the biobank (-80°C). In 2010 homocysteine concentrations were measured in the biobank EDTA plasma samples, from samples taken at baseline (blood samples n=5757, missing n=47) and again at six months. Measurements were done in batches after reduction to the free form with a fluorescence polarization immunoassay on an IMx analyzer (Abbott, Abbott Park, IL, USA).

The median plasma level of homocysteine in The Netherlands (n=1100) was 14.1 µmol/L (IQR 11.8 -17.0), in Scotland (n=2505) 17.9 µmol/L (IQR 15.3-21.8), and in Ireland (n=2152) 18.8 µmol/L (IQR 15.6-23.3). However, there were differences in standard operating procedures per study site, i.e. the Dutch and Scottish blood samples were processed within eight hours, whereas in Ireland this processing frequently exceeded eight hours. Statistical analysis showed that the variance in log homocysteine for Scotland and the Netherlands was comparable (F=2.4, p=0.120), but both showed a significant difference in variance compared with Ireland (Scotland vs. Ireland F=5.4, p=0.020 and the Netherlands vs. Ireland F=11.2, p=0.001). Since plasma homocysteine levels increase by 0.5-1.0 µmol/L per hour in blood at room temperature,[24-26] differences in lag time could explain the differences in variance between Ireland and the other countries. Therefore, we decided to exclude participants from Ireland from this analysis.

Outcomes

The outcomes, described in the design of PROSPER,[23] were the incidence of fatal and nonfatal CHD (including definite or suspected CHD mortality and non-fatal myocardial infarction), non-fatal myocardial infarction (MI), CHD mortality, non-CHD mortality, and all-cause mortality. All CHD endpoints were assessed by the PROSPER Endpoints Committee, which was blinded for study medication and for plasma levels of homocysteine.

Data analysis

At baseline, participants were ranked in three equal groups (low, medium and high homocysteine) based on plasma homocysteine level, sex and study site. Per homocysteine

group, characteristics between placebo and treatment were compared using independent t-tests for continuous data and Pearson Chi-square tests (df=1) for categorical data.

Predictive value of homocysteine in the placebo group
The cumulative incidence rates of fatal and nonfatal CHD and all-cause mortality for the three homocysteine groups are presented in Kaplan-Meier curves and compared with the log rank test (df=2). Hazard ratios (HRs) and corresponding 95% confidence intervals (95% CI) for sex- and study site-specific tertiles of homocysteine were calculated for the endpoints using Cox proportional hazard models (reference low homocysteine), with adjustment for age. To further investigate the independent predictive value of homocysteine, we additionally adjusted for baseline history of cardiovascular disease, for baseline Framingham risk factors [smoking, diabetes, left ventricle hypertrophy, systolic blood pressure, total cholesterol, high density lipoprotein (HDL)] and for earlier published predictors in PROSPER [CRP, HDL and creatinine clearance (Cockcroft-Gault)].

Treatment effect comparing placebo and treatment group
The treatment effects of pravastatin vs. placebo per homocysteine group were calculated with two methods. *First,* per homocysteine group, the cumulative incidence rate for fatal and nonfatal CHD and all-cause mortality are presented for those on placebo and those on pravastatin with Kaplan-Meier curves and compared with the log rank test (df=1) and with Cox proportional hazard models. No adjustments were made. The presence of multiplicative interaction was formally tested by adding the interaction term (treatment x homocysteine group) to the Cox regression model. All analyses were on an intention-to-treat basis.

Second, the absolute risk reduction by treatment with pravastatin was calculated. Differences in absolute risk reductions between the homocysteine groups were tested with a z-test. Numbers needed to treat (NNT) to benefit were calculated over the mean follow-up of the trial (3.2 years) based on the difference in cumulative proportion of surviving in the placebo and pravastatin group.[27;28] Because creatinine clearance seems to be associated with the level of homocysteine, we carried out a subgroup analysis for absolute risk reduction for fatal and nonfatal CHD and for all-cause mortality in people with creatinine clearance ≥30 ml/min.

Influence of treatment with pravastatin on homocysteine
To investigate whether pravastatin treatment influences the plasma levels of homocysteine, we measured homocysteine concentrations after six months treatment for 1832 participants (183 on placebo and 1649 on pravastatin). The effect of treatment of

pravastatin on plasma levels of homocysteine was tested after six months with linear regression analysis, adjusted for baseline homocysteine.

RESULTS

In total, 3620 PROSPER participants from the study sites in The Netherlands and Scotland were eligible for this study. Since 15 participants had missing biobank samples and 83 had missing homocysteine measurements, 3522 participants (1764 placebo and 1758 pravastatin) were included in the analyses. The cut-off values of the homocysteine tertiles (33% and 67%) in the Netherlands (n=1049) were 11.7 and 14.7 μmol/L, respectively, for women, and 13.5 and 16.9 μmol/L, respectively, for men; for Scotland (n=2473) these limits were 15.4 and 19.6 μmol/L, respectively, for women, and 16.9 and 21.0 μmol/L, respectively, for men.

Baseline characteristics

Table 1 presents baseline characteristics of the total group of participants and per homocysteine group, stratified for placebo or pravastatin. In the total group, mean age of the participants was 75 (SD 3.4) years and 48% had a history of cardiovascular disease. The mean homocysteine level at baseline was 18.3 (SD 7.1) μmol/L. Per homocysteine group, there were no differences in baseline characteristics between the pravastatin and placebo groups. Remarkably, the proportion of diabetic patients was lower in the high homocysteine group.

Predictive value of homocysteine in the placebo group

Figure 1 shows the cumulative incidence of fatal and nonfatal CHD and all-cause mortality for the three homocysteine groups within the placebo group. Compared to participants with low homocysteine, those with medium homocysteine had no increased risk of fatal and nonfatal CHD (HR 1.1, 95% CI 0.76–1.6, p=0.569), but those with high homocysteine had a 1.8 fold increased risk (95% CI 1.2–2.5, p=0.001). For overall mortality, the HRs were 1.0 (95% CI 0.67–1.5, p=0.992) and 1.7 (95% CI 1.2–2.5, p=0.003), respectively. These estimates did not change by additional adjustments for history of cardiovascular disease, for Framingham Risk Factors, and for CRP, HDL and creatinine clearance (data not shown).

Similarly, participants with high homocysteine also had an increased risk for non-fatal MI, CHD mortality and non-CHD mortality. Furthermore, for all these outcomes no differences in risk were found between the medium and low homocysteine groups (data not shown). t

Table 1. Baseline characteristics of the participants stratified for treatment per homocysteine group (n=3522).

| | All | Homocysteine group | | | | | |
| | | Low | | Medium | | High | |
	n=3522	Placebo n=597	Pravastatin n=575	Placebo n=579	Pravastatin n=598	Placebo n=588	Pravastatin n=585
Demographic and functional characteristics							
Study site Scotland	2473 (70)	424 (71)	400 (70)	400 (69)	425 (71)	416 (71)	408 (70)
Men	1765 (50)	296 (50)	291 (51)	286 (49)	304 (51)	285 (49)	303 (52)
Age (years)	75 (3.4)	75 (3.4)	75 (3.3)	75 (3.2)	75 (3.3)	76 (3.5)	76 (3.4)
Mini-Mental State Examination (points)	28 (1.5)	28 (1.4)	28 (1.4)	28 (1.4)	28 (1.5)	28 (1.5)	28 (1.6)
Barthel index (points)	20 (0.7)	20 (0.7)	20 (0.8)	20 (0.7)	20 (0.5)	20 (0.8)	20 (0.9)
Instrumental activities of daily living (points)	14 (0.9)	14 (0.9)	14 (0.9)	14 (0.9)	14 (0.7)	14 (1.1)	14 (1.0)
Clinical history and cardiovascular risk factors							
History of cardiovascular disease*	1675 (48)	267 (45)	272 (47)	269 (47)	279 (47)	298 (51)	290 (50)
History of diabetes mellitus	386 (11)	88 (15)	85 (15)	68 (12)	57 (9.5)	45 (7.7)	43 (7.4)
Creatinine clearance <30 ml/min†	96 (2.7)	12 (2.0)	15 (2.6)	14 (2.4)	16 (2.7)	17 (2.9)	22 (3.8)
Body mass index (kg/m²)	27.0 (5.5)	27 (5.6)	27 (5.5)	27 (5.7)	27 (5.3)	27 (5.6)	27 (5.4)
Current smoker	943 (27)	157 (26)	137 (24)	156 (27)	166 (28)	167 (28)	160 (27)
Alcohol (units per week) ‡	5.3 (8.4)	4.9 (7.3)	5.0 (7.5)	5.5 (8.7)	5.6 (9.5)	4.9 (7.7)	5.7 (9.4)
Systolic blood pressure (mmHg)	155 (21)	153 (21)	154 (21)	156 (21)	154 (21)	155 (23)	155 (22)
Total cholesterol (mg/dl)	221 (35)	218 (35)	220 (36)	221 (34)	222 (35)	220 (36)	224 (37)
LDL cholesterol (mg/dl)	148 (31)	147 (31)	148 (30)	149 (30)	149 (31)	148 (32)	151 (32)
HDL cholesterol (mg/dl)	49 (13)	50 (13)	49 (13)	49 (13)	49 (13)	49 (15)	49 (14)
Triglycerides (mg/dl)	137 (61)	131 (59)	138 (63)	136 (59)	140 (66)	136 (61)	137 (58)
Homocysteine (μmol/L)	18.3 (7.1)	13.0 (2.1)	13.1 (2.1)	16.8 (2.2)	17.0 (2.2)	25.2 (8.6)	24.6 (8.2)

n (%) or mean (SD)

*Any of stable angina, intermittent claudication, stroke, transient ischaemic attack, myocardial infarction, peripheral arterial disease surgery, or amputation for vascular disease ≥6 months before study entry.

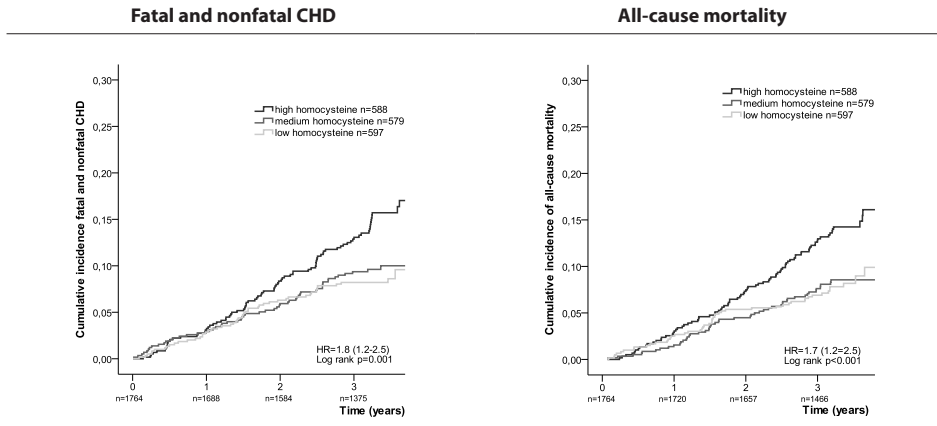†Calculated with the Cockroft-Gault formula; ‡1 unit = 60 ml distilled spirits, 170 ml wine or 300 ml beer

Fatal and nonfatal CHD   **All-cause mortality**

Figure 1. Cumulative incidence of fatal and nonfatal CHD and all-cause mortality depending on baseline plasma levels of homocysteine in the placebo group (n=1764).
HR=Hazard ratio (95% CI) high homocysteine group vs. low homocysteine group, adjusted for age.

Treatment effect depending on homocysteine

Figure 2 presents the cumulative incidence of fatal and nonfatal CHD and all-cause mortality in participants with and without pravastatin per homocysteine group. In participants with high homocysteine, an HR of 0.57 (95% CI 0.41–0.81, p=0.002) was found as treatment effect of pravastatin on fatal and nonfatal CHD, and an HR of 0.70 (95% CI 0.50–0.98, p=0.036) as treatment effect on all-cause mortality. In medium and low homocysteine, there was no significant difference in cumulative incidence between placebo and pravastatin treatment. Formal testing of multiplicative statistical interaction was not significant (Figure 2). Similar patterns were seen for non-fatal MI and CHD mortality. For non-CHD mortality, we found no effect of treatment with pravastatin in all three homocysteine groups (data not shown).

Table 2 presents absolute treatment effects of pravastatin per homocysteine group. The absolute risk reduction in fatal and nonfatal CHD by pravastatin treatment was 1.6% (95% CI -1.6–4.7) in the low homocysteine group, and 6.7% (95% CI 2.7–10.7) in the high homocysteine group (absolute risk reduction difference 5.2%, 95% CI 0.11–10.3, p=0.046). For all-cause mortality the absolute risk reductions were -0.66% (95% CI -4.0–2.7) and 4.6% (95% CI 0.78–8.4), respectively (absolute risk reduction difference 5.2%, 95% CI 0.19-10.3, p=0.042).

In persons with creatinine clearance ≥30 ml/min (n=3426) we found a mean homocysteine value of 18.3 µmol/L and in persons with creatinine clearance <30 ml/min (n=96) a mean homocysteine value of 19.0 µmol/L (p=0.292). Because creatinine clearance is known to be associated with the level of homocysteine we carried out a subgroup

analysis in persons with creatinine clearance ≥30 ml/min. The absolute risk reductions by pravastatin treatment remained similar (fatal and nonfatal CHD 6.0% (95% CI 0.84–11.1, p=0.023) and all-cause mortality 5.8% (95% CI 0.70–11.0, p=0.026)).
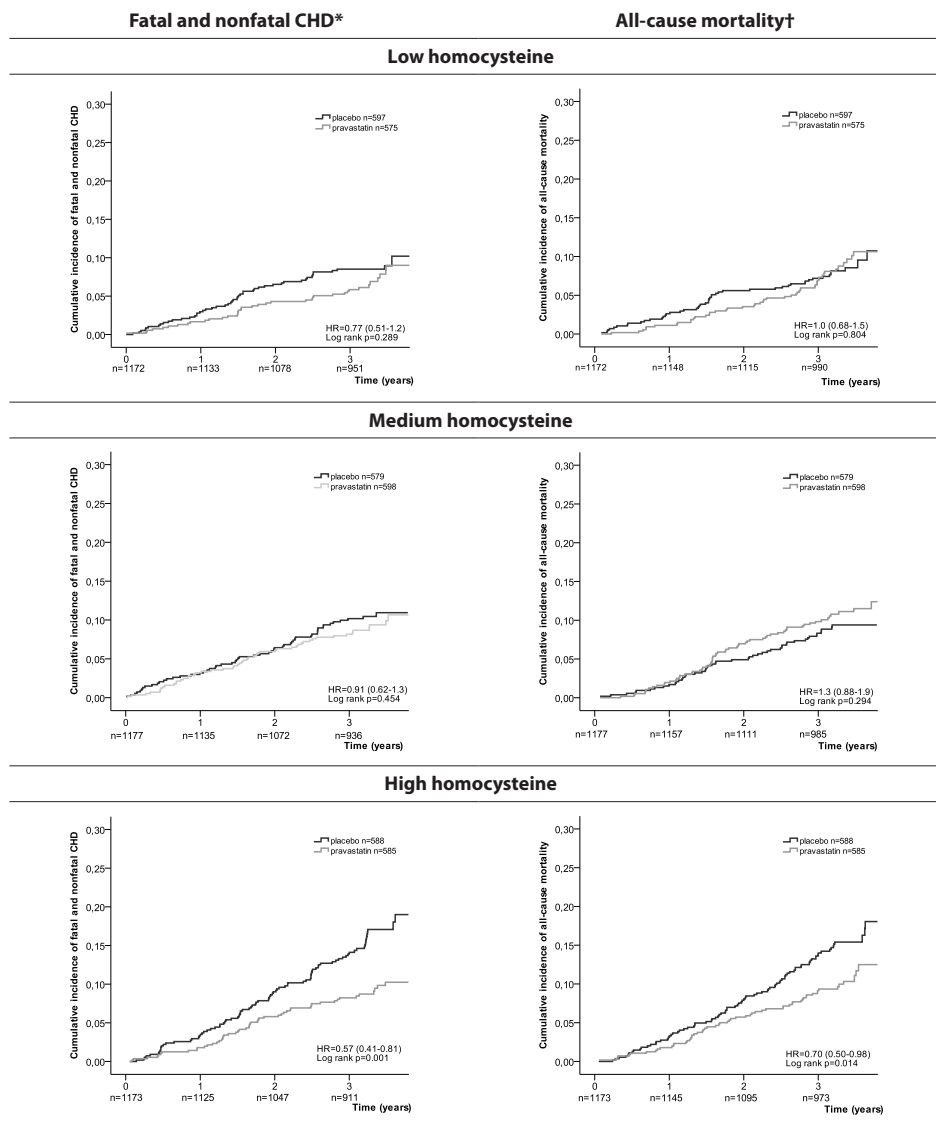
Fatal and nonfatal CHD*   **All-cause mortality†**

Low homocysteine

Medium homocysteine

High homocysteine

Figure 2. Cumulative incidence fatal and nonfatal CHD and all-cause mortality depending on pravastatin treatment, stratified for plasma levels of homocysteine at baseline.
*p for multiplicative interaction = 0.208
†p for multiplicative interaction = 0.097

Table 2. Absolute effect of treatment with pravastatin on cardiovascular outcomes and mortality after 3.2 years per homocysteine group.

Outcomes	Homocysteine groups*	Placebo		Pravastatin		ARR (95% CI)	Diff ARR (95% CI)	p
		n	% events (95% CI)	n	% events (95% CI)			
Fatal and nonfatal CHD	Low	48	8.2 (6.0–10.5)	32	6.7 (4.5–8.9)	1.6 (-1.6–4.7)		
	Medium	54	9.9 (7.4–12.4)	47	8.7 (6.3–11.0)	1.2 (-2.2–4.7)	-0.32 (-5.0–4.3)	0.889
	High	76	15.9 (12.8–19.1)	47	9.2 (6.7–11.7)	6.7 (2.7–10.7)	5.2 (0.11–10.3)	0.046
Non-fatal MI	Low	29	5.1 (3.3–6.9)	26	5.6 (3.6–7.7)	-0.5 (-3.2–2.2)		
	Medium	39	7.3 (5.1–9.5)	26	5.1 (3.2–7.0)	2.2 (-0.73–5.0)	2.7 (-1.3–6.7)	0.184
	High	51	11.3 (8.5–14.1)	32	6.4 (4.3–8.5)	4.9 (1.4–8.4)	5.5 (1.0–9.9)	0.016
CHD mortality	Low	20	3.4 (1.9–4.9)	11	2.0 (0.83–3.2)	1.4 (-0.45–3.3)		
	Medium	18	3.3 (1.8–4.7)	27	4.7 (3.0–6.4)	-1.5 (-3.7–0.83)	-2.9 (-5.8–0.08)	0.057
	High	33	6.5 (4.4–8.6)	18	3.5 (1.9–5.1)	3.0 (0.35–5.6)	1.5 (-1.7–4.8)	0.347
Non-CHD mortality	Low	25	4.8 (3.0–6.6)	31	6.9 (4.6–9.1)	-2.1 (-4.9–0.84)		
	Medium	30	5.4 (3.5–7.3)	32	5.9 (3.9–7.8)	-0.46 (-3.2–2.3)	1.6 (-2.4–5.6)	0.430
	High	46	8.4 (6.1–10.7)	34	6.5 (4.4–8.5)	2.0 (-1.2–5.1)	4.0 (-0.24–8.2)	0.064
All-cause mortality	Low	45	8.0 (5.8–10.3)	42	8.7 (6.3–11.1)	-0.66 (-4.0–2.7)		
	Medium	48	8.5 (6.2–10.8)	59	10.3 (7.8–12.8)	-1.8 (-5.2–1.6)	-1.1 (-5.9–3.6)	0.638
	High	79	14.3 (11.4–17.2)	52	9.8 (7.3–12.2)	4.6 (0.78–8.4)	5.2 (0.19–10.3)	0.042

*Group sizes: low: placebo n=597, pravastatin n=575; medium: placebo n=579, pravastatin n=598; high: placebo n=588, pravastatin n=585

% events (95% CI) = Cumulative incidence of events after 3.2 years with corresponding 95% confidence intervals

ARR (95% CI) = Absolute risk reduction in % with corresponding 95% confidence intervals

Diff ARR (95% CI) = Difference in absolute risk reduction in % with corresponding 95% confidence intervals compared to reference group low homocysteine

p-value of difference in absolute risk reduction compared to reference group low homocysteine estimated by z-test
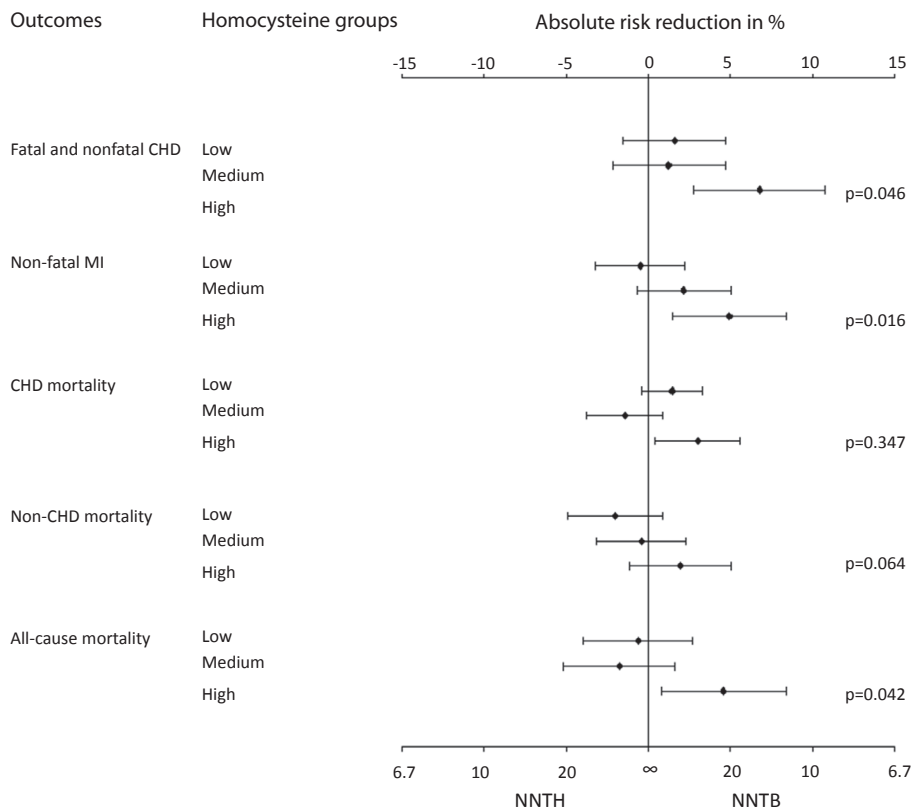
Figure 3. Number needed to treat with pravastatin after 3.2 years dependent on homocysteine level at baseline.
NNTH= Number needed to treat to harm
NNTB= Number needed to treat to benefit
CHD=coronary heart disease; MI=myocardial infarction
p-value of difference between high and low homocysteine group for absolute risk reduction in % and for number needed to treat estimated by z-test

For fatal and nonfatal CHD the NNT with pravastatin to benefit for 3.2 years is 14.8 (95% CI 9.3–36.6) in the high homocysteine group, 81.3 (95% CI 21.5–∞) in the medium group, and 64.5 (95% CI 21.4–∞) in the low homocysteine group (p high vs. low=0.046) (Figure 3). For all-cause mortality we found a beneficial result in the high homocysteine group (NNT 21.8, 95% CI 11.9–129), but no benefit in the medium and low homocysteine groups (p high vs. low=0.042).

Influence of pravastatin on homocysteine

After six months treatment, the difference in homocysteine levels was -0.52 μmol/L (95% CI -1.1–0.07) for those on pravastatin compared to baseline (linear regression, p=0.082).

DISCUSSION

This study suggests that homocysteine may be a promising new CHD risk predictor in older people, since high plasma homocysteine not only selects older persons at high risk for fatal and nonfatal CHD and all-cause mortality, but also identifies those with the highest absolute risk reduction by pravastatin and lowest NNT to prevent fatal and nonfatal CHD.

Earlier studies showed that older persons with high levels of homocysteine are at increased risk for cardiovascular events and homocysteine level may provide additional risk stratification beyond traditional risk factors.[13-18] For example, Veeranna et al. examined whether adding homocysteine to a model based on traditional cardiovascular disease risk factors improved classification. In two younger population cohorts, they found that addition of homocysteine level to the Framingham Risk Score significantly improved risk prediction.[18] Moreover, for persons aged 85+ years, De Ruijter et al. showed that the classic risk factors as included in the Framingham Risk Score no longer accurately predicted cardiovascular mortality in those with no history of cardiovascular disease, while a single measurement of homocysteine did accurately identify those at high risk of cardiovascular mortality.[13] Our findings not only confirm studies reporting that homocysteine predicts CHD risk in old age, but also show the independent predictive capacity in a selected population of older persons with increased cardiovascular risk. A recent meta-analysis showed that a moderate homocysteine elevation due to genetic variance does not meaningfully affect CHD risk.[29] This finding indicates that circulating homocysteine levels within the normal range are not causally related to CHD risk. Moreover, large RCTs and their meta-analyses show that lowering plasma homocysteine by treatment with folate has no beneficial effect on the incidence of cardiovascular events.[16;20;21] Therefore, the underlying biological pathway to explain predictive value of high homocysteine for cardiovascular diseases, if there is one, to date is still unknown. Homocysteine may be seen as an epiphenomenon rather than a causal agent, but this does not refute its predictive abilities.

Since homocysteine showed to be not causally related to cardiovascular disease, it was unknown if preventive treatment could be offered to those with high homocysteine to reduce their cardiovascular risk. In the AFCAPS/TexCAPS study,[30] with only a small proportion of old individuals, the beneficial effect of statin treatment in people with elevated homocysteine levels was limited to people with an LDL level higher than 149 mg/dL. Our results further extend the findings from the AFCAPS/TexCAPS study by demonstrating that the benefits of statin treatment may differ by homocysteine levels among high-risk patients with an average LDL level of 148 mg/dl. If these findings hold

true in a subsequent study, there could be a role for measurement of homocysteine levels to help guide decisions on statin use in older individuals, which is a widely available treatment, also for older persons. This is an important criterion of Wilson and Jungner underlying screening.[19]

The present study revealed other findings that deserve further examination. First, although we only found a clear CHD risk benefit from pravastatin therapy over the trial period of 3.2 years in older persons with high homocysteine and not in older persons with low and medium homocysteine, we did not find multiplicative interaction for the treatment effect. Therefore, there is a possibility that pravastatin has the same treatment effect in the three homocysteine groups. However, even when the relative treatment effect is similar between these groups, those at highest absolute risk will have most benefit expressed in absolute risk reduction. This absolute risk reduction and corresponding NNT is very important in clinical practice and guidelines, since this indicates the number of persons who need to be treated in order to prevent one event.

Second, the effect of pravastatin over the homocysteine groups does not show a linear trend. This finding could be explained by a lack of power due to a small number of events in the low and medium homocysteine groups, therefore a possibility of random variation cannot be excluded. However, it is also possible that pravastatin therapy is only effective in people with homocysteine beyond a certain cut-off value. The possibility of absolute cut-off values requires more in-depth study, investigated in a population with consistent blood sampling and storage procedures.

Third, we found that plasma levels of homocysteine did not change significantly with pravastatin treatment during a six-month period, although a small reduction was seen. Further examination is needed to determine the effect of pravastatin treatment on homocysteine levels. If pravastatin does not affect the homocysteine level, homocysteine measurement might be useful to evaluate the need for continuing cardiovascular preventive therapy in persons under pravastatin treatment.

For new biomarkers, others have investigated whether high cardiovascular risk and corresponding benefit from treatment could be predicted. A large-scale RCT[31] and an earlier analysis in PROSPER[32] showed that baseline C-reactive protein concentration predicts cardiovascular risk, but does not predict the relative CHD risk benefits of pravastatin therapy. Other analyses in PROSPER showed that high-density lipoprotein[33] and creatinine clearance[34] can predict benefit for prevention of fatal and nonfatal CHD by pravastatin therapy. However, a high plasma level of homocysteine remained predictive for a beneficial effect of pravastatin even in persons with creatinine clearance ≥30 ml/

min. Furthermore, pravastatin was more effective in preventing cardiovascular events in those without diabetes.[22] We showed that adjustment for these predictors did not influence the predictive value of homocysteine. A next step is to study the clinical value of homocysteine and other biomarkers by comparing their predictive value in combination with treatment response, to develop the most effective predictors of cardiovascular risk and treatment benefit. This is particularly important since statins are not without side-effects or costs, and targeting those at maximal risk and with most to gain would be both clinically and economically advantageous.

Strength and limitations

This study was embedded in the PROSPER trial, a large double-blinded randomized placebo-controlled trial in older persons. This landmark clinical cardiovascular trial with older participants was performed following guidelines of good clinical practice, including endpoints that were uniformly assessed by the Endpoint Committee. Since homocysteine was assessed after closure of the trial, plasma levels of homocysteine had no influence on the study procedures, clinical treatment during follow-up, or on the decisions of the Endpoint Committee.

A limitation of this study is that the PROSPER study procedures were not originally designed to collect optimal blood samples for the assessment of plasma homocysteine. Therefore, it was appropriate to use data from only two of the three PROSPER study sites. However, in these two sites, it is still possible that some samples were stored at room temperature until maximally eight hours before processing. Since this could lead to misclassification, that was assumed to be non-differential, this could have resulted in underestimation of the differences in treatment effect by homocysteine levels. Because it is also known that homocysteine levels vary between countries,[13;35;36] more studies are needed to validate the absolute cut-off values of homocysteine to select elderly at highest risk in clinical practice. Moreover, data about the use of B vitamins, that lower the levels of homocysteine, are not available. Another limitation of this study is that the treatment-by-homocysteine group multiplicative interaction was not significant, although the absolute risk reduction by high versus low homocysteine was significant (p=0.046 for fatal and nonfatal CHD and p=0.042 for all-cause mortality). The possibility of a type 1 error from multiple comparisons cannot be excluded. It might also be seen as a limitation that these analyses focused only on the value of homocysteine to predict the CHD risk and treatment effect, rather than investigating the etiological mechanisms behind our findings. Predictive and etiological studies will contribute to the further development of cardiovascular risk management in old age, both on their own merits.

Implications

A recent analysis on cost-effectiveness of statin treatment in primary care showed that even in high age groups it is useful to stratify for risk of cardiovascular outcomes.[12] Our study shows that homocysteine may usefully predict CHD risk in the PROSPER population of old persons with increased cardiovascular risks. As a consequence, individuals without traditional risk factors and, thus, with the lowest risks were excluded. Before these results can be implemented in current guidelines, further research is needed to find a cutoff value of homocysteine and confirm that high-risk older adults with high homocysteine levels get more benefit from pravastatin treatment. Moreover, whether homocysteine is useful in predicting benefits from pravastatin treatment for low-risk or intermediate-risk older adults remains to be investigated.

In conclusion, homocysteine is a promising CHD risk predictor in old age, not only because high plasma homocysteine identifies older persons at high risk for fatal and nonfatal CHD, but also because those persons have the highest absolute risk reduction by pravastatin treatment and lowest number needed to treat to prevent fatal and nonfatal CHD. This is an important step in the further development of CHD risk stratification and treatment for older people.

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Chapter 8

General discussion

GENERAL DISCUSSION

Preventive care traditionally refers to measures taken to prevent disease and injury and, generally, not to less well-defined goals such as maintenance of independence and wellbeing. With old age, however, the prevalence of ailments and chronic diseases increases, leading to a decrease in independence and wellbeing. Because older people differ considerably from each other with regard to health and functional status, a 'one size fits all' program for prevention is not possible. For some subgroups, preventive care might be used to enable people to live as independently as possible by preventing or postponing disability and social isolation. For others, prevention of disease to lengthen life expectancy will probably be the most suitable aim. Moreover, preventive programs can be organized collectively as well as individually. These two dimensions of preventive care for older people are described in Chapter 1. In short, it remains unclear which approach and which aim will be most appropriate in preventive care for older people. However, it is possible that specific subgroups of older people can be identified who will need the same approaches for the same aims. This chapter discusses the possibilities to develop strategies (varying in their aim and approach) in preventive care for older people and makes some recommendations for clinical practice and future research.

1. Exploration of aims in preventive care for older people

Is there scientific support for the idea that the aim of prevention is not only to prevent disease and injury, but also to maintain independence and wellbeing?
In current health policy [1-4] much attention is directed to the older population. The aging society implies that more people will be dependent on caregivers and healthcare facilities. Health care for older persons might contribute to the maintenance of good physical and mental health, and might help older people to stay independent and participate in social activities for a longer period of time. It is important to develop strategies in health care for older people which not only contribute to their life expectancy but also help to maintain their daily functioning and wellbeing. Therefore, it is necessary to investigate whether preventive strategies can indeed contribute to these aims.

Chapter 2 shows that general practitioners (GPs) believe that preventive care can contribute to life expectancy and to functioning in daily life and wellbeing. According to GPs, the focus of preventive care for their older patients depends on the level of vitality of the individual person, rather than on their age. In all discussions, the level of vitality as perceived by the GP tends to influence their ideas about preventive care. When older people become less vital and thus more vulnerable, the scope of preventive care supplied by the GP shifts from a 'disease model' to a 'functional model', and from mainly cardiovascular risk management to preventing functional decline. These findings reveal

that GPs believe that vulnerable older people require a prevention strategy that differs from that for vital older people; however, it is not known to what extent this idea actually mirrors the behavior of GPs. Current international screening guidelines[5-13] tend to ignore a differentiation in aims that depend mainly on patient characteristics. Therefore, it is also unknown whether screening can contribute to the prevention of functional decline in older people.

In Chapter 5 evidence for the contribution of screening to the prevention of functional decline in older persons was investigated and the outcomes were stratified for three age groups (60-74, 75-84 and 85-plus years) and three levels of vitality, i.e. for the general population, and for the population divided into vital and vulnerable persons. The appropriateness of screening was assessed by an expert panel using the RAND/UCLA method. In general, the panelists appreciated the idea to investigate the contribution of screening to the maintenance of independence and wellbeing, whereas until then screening was mainly applied to the prevention of disease. The panelists considered vulnerability to be an important factor in the determination of the appropriateness of screening to maintain independence and wellbeing, whereas age scarcely influenced the appropriateness of screening. Although, according to current knowledge, evidence for the value of screening vulnerable people is still lacking, the panelists expect benefits for (in particular) vulnerable people when more tests and interventions are developed for this specific group. This conclusion is in accordance with the ideas presented by the GPs (Chapter 2).

In conclusion, many health policies aim at the maintenance of independence and wellbeing for older people. GPs and other professionals in geriatric care also consider this aim to be relevant for prevention, but the appropriateness of this aim appears to depend on the level of vitality of the individual older person. Therefore, maintenance of independence and wellbeing is an important aim in preventive care, complementing the traditional aim of prevention of disease. Especially in older vulnerable individuals, professionals expect that preventive care can contribute to the maintenance of independence and wellbeing.

2. Maintenance of independence and wellbeing

a. Is it possible to identify older people who will benefit from a preventive approach which contributes to the maintenance of independence and wellbeing?

To develop preventive strategies to maintain independence and wellbeing, screening instruments are needed to identify vulnerable older people at high risk for deterioration in the near future. It is known that chronic diseases [14-20] and multimorbidity[19-21] are strongly related to disability. Moreover, although a variety of tools are available to

measure vulnerability in various ways,[22-28] there is no standardized and valid method to screen for manifestations of vulnerability.

In the discussions in the focus group study, the GPs appeared to be able to differentiate between vulnerable and vital older persons (Chapter 2), even though no definitions for 'vital' and 'vulnerable' were specified. Interestingly, during the discussions there was no confusion between the GPs regarding these two categories of older persons; it seems that the GPs used an implicit concept of vulnerability. Perhaps GPs share a unique perspective as to what defines vulnerability; on the other hand, perhaps they remained unaware of actual distinctive perspectives related to the concept 'vulnerability'. Therefore, the variability between GPs in their assessment of vulnerability was studied in Chapter 4. In the RAND study (Chapter 5), the expert panel started their discussion by formulating a definition of vulnerable persons, i.e. older people with (simultaneously) a high prevalence of diseases/disorders, a poorer prognosis, disability of various kinds, and multiple problems. These general characteristics appeared to be sufficient for the expert panel to discuss and assess the appropriateness of the screening topics.

Due to the lack of a gold standard for the selection of vulnerable older people at risk for functional decline, we investigated two ways to predict the vulnerability of older persons. In the first study (Chapter 3) the predictive value of multimorbidity was explored for its association with an increase in disability over time and the role of cognitive impairment in this association. The Leiden 85-plus Study, a population-based study of individuals aged 85-plus (Chapter 3) with a 5-year follow-up, showed that the predictive value of multimorbidity for an increase of disability in activities in daily living (ADL) varies with cognitive function in very old people. Remarkably, multimorbidity predicted an accelerated increase of disability in ADL only in older people with a Mini-Mental State Examination (MMSE) score ≥28 points at baseline. In persons with a lower MMSE score this predictive relation was not present, possibly because the cognitive problems dominated the functionality. This implies that the prevalence of multimorbidity in older people (a relatively easy measurement for GPs) is an indicator for risk in deterioration of ADL performance in only 35% of this age group, because 65% of the 85-plus population no longer has an MMSE score ≥28 points. Therefore, preventive programs to promote older people to live as independently as possible cannot be based on multimorbidity as the sole selection criterion. At least a two-stage screening test is needed, which encompasses cognition screening as a first step and multimorbidity screening as the second, in order to select older people at increased risk for disability.

Since the effect of cognitive impairment seems to dominate the effect of multimorbidity on ADL performance, in clinical practice the cognitive function of older people is

probably a better predictor of increased disability in ADL than multimorbidity. To select people with cognitive impairment using the MMSE measurement is a relatively complex strategy, partly because MMSE measurement is labor-intensive and also costly. It is questionable whether a formal MMSE measurement is needed to select people with optimal cognitive function. Most likely GPs know their patients well enough to classify them by 'gut feeling' into those with and without optimal cognitive function. In this way they can limit testing to those for whom there is some doubt about their level of cognitive functioning.

GPs seem to apply an intuitive gut feeling in various clinical situations. Stolper et al.[29] reported that a gut feeling can produce a 'sense of alarm'; this is defined as an uneasy feeling perceived by GPs when they become concerned about a possible adverse outcome, even when a specific indication is lacking. '*There's something wrong here*' seems to be the sense of alarm that activates the diagnostic process of GPs and motivates them to initiate specific management to prevent serious health problems. A prerequisite for this gut feeling is sufficient knowledge of the person and, for several issues, this requires long-term observation (to establish a decline/irregularity). This stresses the need for regular consultation with or visits to older patients.

Similarly, the notion of 'vulnerability' may also be a concept such as gut feeling. GPs seemed to share a unique perspective as to what constitutes vulnerability (Chapter 2), without a need for explicit criteria or a gold standard. Chapter 4 examines variability in the assessment of vulnerability between GPs to determine whether GPs indeed share a uniform concept of vulnerability. The percentage of patients aged 75-plus assessed as being vulnerable by the GP varied per GP: median 32.0% (IQR 19.5 to 40.1%, range 2.4 to 81.0%). This variation was not only due to differences in the case mix of their patients, but also to differences in the weighing that GPs attribute to some patient characteristics in the assessment of vulnerability. GPs were similar in the way they took into account patient characteristics in the medical and psychological domains in their vulnerability assessment, but differed in the way that they weighed the functional status. These findings might be attributed to differences in the education of GPs and the corresponding focus on diseases. More uniformity might be achieved when GPs receive additional training in the use of a functional model as concept of care.

In conclusion, these two studies support the possibility to select older people at risk for deterioration in functioning, as well as older people who are vulnerable according to assessment by GPs. However, more studies are needed to compare the outcomes of the vulnerability assessment by GPs with those of existing tools that measure vulnerability. These analyses might reveal the additional value of screening tools compared

to the assessment by GPs (which is simple, not costly and apparently reliable). When stratification on vulnerability becomes feasible this will allow to select older individuals that, according to GPs (Chapter 2), may benefit from preventive care to maintain their independence and wellbeing.

b. Which preventive strategies are appropriate to contribute to the maintenance of independence and wellbeing?

The previous section discussed the possibility to select vulnerable older persons and this section examines the usefulness of stratification on vulnerability. The next step is to explore whether preventive activities are available for the group of people who require maintenance of independence and wellbeing. According to the GPs in the focus group discussions (Chapter 2), preventive care for vulnerable people requires an individualized approach to prevent functional decline. However, the RAND study investigated whether a collective approach could be appropriate to maintain independence and wellbeing (Chapter 5). The appropriateness of screening older people to prevent functional decline was studied and the outcomes were stratified for levels of vitality status, i.e. the overall general population, and a population divided into vital and vulnerable older persons. The appropriateness was assessed by an expert panel using the RAND/UCLA appropriateness method. In order to conclude that screening to prevent functional decline is appropriate, the screening must at least (in general) approximately meet the criteria described by Wilson and Jungner.[30] When evidence on fulfilling the criteria of Wilson and Jungner was lacking or inconclusive, the experts' opinions regarding a potential benefit to prevent functional decline were taken into account.

Despite increasing interest in screening of community-dwelling older people and the recommendations in guidelines, the expert panel considered screening to maintain independence and wellbeing to be appropriate for only a few conditions. Screening for insufficient physical activity in order to prevent functional decline was considered appropriate for all older persons, without a distinction being made between the level of vitality or age. Screening for cardiovascular risk factors and smoking status is considered useful for the general older population aged 60-74 years. In the higher age groups, however, screening for cardiovascular risk factors and smoking faces lack of evidence, because the traditional risk factors no longer accurately predict the cardiovascular risk.[31] There was insufficient evidence to support screening for the other investigated conditions. Interventions that merely stimulate wellbeing (e.g. interventions dealing with loneliness) were not considered to be supported by strong evidence. However, based on experience, the expert panel expected at least some benefit from these interventions for the vulnerable population. For 11 of the 29 investigated conditions, the expert panel was uncertain about the appropriateness of screening vulnerable older persons, whereas

they considered screening of older people with good vitality for the same condition to be inappropriate. Since the majority of vulnerable older persons already receive medical care for their chronic disease(s), the expert panel expected more benefit to be derived from improving regular medical care than from a separate screening program.

In conclusion, to maintain independence and wellbeing, it is recommended to distinguish between vital and vulnerable older people, because most benefit is expected in the vulnerable population. However, screening for disorders/ailments might not be the appropriate preventive strategy to contribute to the maintenance of independence and wellbeing: there is little evidence for such a collective approach and a separate screening program might not be the appropriate strategy for vulnerable older persons. Preventive care for vulnerable older people probably needs a more individualized approach within the structure of regular care.

3. Prevention of disease, focusing on cardiovascular disease

a. Is it possible to identify subgroups by screening older people to prevent disease?
The focus group study (Chapter 2) revealed that, apart from the national cancer screening (breast/colon cancer) and vaccination programs, cardiovascular risk management is considered the main topic in disease prevention. Chapter 5 shows that cardiovascular risk management based on risk stratification appeared to be appropriate in the general and vital older population aged 60-74 years to maintain independence and wellbeing, although there was uncertainty regarding the vulnerable population. In the general and vital older population cardiovascular risk management is considered to be appropriate because it increases life expectancy in these groups and prevents a cardiovascular disease-related decrease in functional status. In vulnerable older people, however, healthcare professionals did not reach agreement: some rated cardiovascular screening as appropriate and others as inappropriate. However, if cardiovascular risk management is not applied in this group, not only will the number of cardiovascular deaths increase but so will the number of non-fatal cardiovascular diseases, with a further decrease in functional status and wellbeing in this population. Therefore, selecting subgroups of older people based on risk stratification for cardiovascular disease and death will (potentially) be appropriate for both vital and vulnerable persons because cardiovascular risk management prevents death and contributes to the maintenance of independence and wellbeing. However, the traditional cardiovascular risk management based on classic risk factors (like the Framingham Risk Score) is appropriate for people aged ≤75 years but is not applicable for those older than 75 years.[31]

The Leiden 85-plus Study (Chapter 6) investigated the possibility to select subgroups of older people at high risk for cardiovascular morbidity and mortality. In very old

community-dwelling people, differences in prognosis between those with various levels of prevalent cardiovascular disease were compared with those with no manifest cardiovascular disease. The prognosis was studied not only regarding incident cardiovascular morbidity and mortality, but also with respect to functional status. Participants with a history of major cardiovascular disease had a markedly increased risk of recurrent myocardial infarction, stroke and functional decline, as well as cardiovascular and all-cause mortality. Patients with a history of minor cardiovascular disease had a relatively better prognosis. Therefore, the extent of the cardiovascular disease history is an easy screening tool for clinicians to identify patients at high risk for new cardiovascular events, functional decline and cardiovascular mortality, as well as all-cause mortality. These results encourage both physicians and very old patients with a history of major cardiovascular disease to maximize their cardiovascular preventive efforts. However, when adverse effects/harmful interactions arise in very old patients with minor cardiovascular disease, the balance between benefit and harm might change and strict continuation of preventive medication might be reconsidered. In the future other cardiovascular risk markers might be identified with better high-risk selection mechanisms; however, this study shows that even in very old age, risk stratification for cardiovascular morbidity/mortality is possible in the general older population.

b. Is a high-risk approach an appropriate preventive strategy to contribute to prevention of cardiovascular disease in older persons?

The next question to be addressed is whether a high-risk approach not only selects people with the highest risk of events, but also those who will derive the most benefit from preventive cardiovascular treatment. Earlier studies showed that even in the general older populations, preventive cardiovascular treatment is still effective.[32;33] To investigate whether preventive cardiovascular intervention is more effective in subgroups of older people at highest risk, the effect of preventive pravastatin treatment was investigated in three groups at risk for cardiovascular disease stratified on their plasma levels of homocysteine. Earlier, De Ruijter et al. showed that in older persons stratification based on homocysteine presents a possibility to select those at high cardiovascular risk.[31] To investigate the effect of preventive treatment in these subgroups, a post-hoc subgroup analysis was performed in PROSPER[33] (a large double-blinded randomized placebo-controlled trial) to assess the effect of pravastatin on risk for coronary heart disease and mortality in older persons, stratified for plasma levels of homocysteine. Since homocysteine was shown not to be causally related to cardiovascular disease, it was unknown which preventive treatment could be offered to those with high homocysteine to reduce their cardiovascular risk. In that study, the non-causal relationship between homocysteine and effect of pravastatin was investigated. Although it is customary, a causal relation between the predictor and the predicted status is not required.

This study revealed that homocysteine may be a promising new coronary heart disease risk predictor in older people, since high plasma homocysteine not only selected older persons at high-risk for (non)fatal coronary heart disease and all-cause mortality, but also identified those with the highest absolute risk reduction by pravastatin and the lowest number needed to treat to prevent non(fatal) coronary heart disease. When the high-risk population which benefits most from cardiovascular-preventive intervention can be selected, this approach might be appropriate for the vital and vulnerable part of the older population. Since preventive cardiovascular treatment contributes to life expectancy and prevention of functional decline, it contributes to both of the aims described in this thesis: prevention of disease, and maintenance of independence and wellbeing. This research shows that, to prevent diseases, it is possible to select high-risk groups with the most benefit from preventive treatment in the general older population; however, more research is needed to develop the optimal screening and treatment strategies.

Conclusion

There is scientific support for the idea that the aim of prevention in older people is not only to prevent disease and injury, but also to maintain independence and wellbeing. Different strategies and subgroups can be identified for these aims (Figure 1). The aim to maintain independence and wellbeing seems to be appropriate for the vulnerable population. Although there is no gold standard to stratify for vulnerability in the general older population, GPs seem to share the same concept of vulnerability for somatic and psychological patient characteristics. Moreover, the variability between GPs will probably decrease further after additional training in the functional model. Perhaps there will not be one 'best' overall selection strategy for vulnerability, but perhaps selection will depend on the intended interventions. Within the vulnerable older population there is no evidence (except for physical activity) that a collective screening approach, with a standardized intervention program, will be the appropriate way to contribute to the maintenance of independence and wellbeing. This implies that the effort spent in preventive health centers for seniors will probably not be effective. Chapter 1 described that preventive health centers for seniors can be placed in the lower left quadrant of Figure 1, because they use a collective approach to maintain independence and wellbeing.[7;34] Since the collective approach seems to be an inappropriate strategy to contribute to this aim, it is doubtful whether these health centers fulfill the purpose for which they were established. Moreover, it is questionable whether early detection and prevention of specific disorders like comorbidity, the responsibility of local authorities according to the Dutch Public Health Act, can be organized collectively with a standardized, programmatic approach. The limited budgets available for preventive care and research can probably be better spent on more promising activities, i.e. those in the upper left

and lower right quadrants. Since the majority of vulnerable older people already receive medical care for their chronic disease(s), more benefit can be expected from improving the individual regular care (in the lower right quadrant) than from a separate screening program. The ISCOPE study (a cluster-randomized controlled trial investigating the effect of pro-active care to patients with complex problems aged ≥75 years) explored this individualized approach among vulnerable older people. Moreover, the 'gut feeling' of GPs in their selection of older people for interventions to maintain independence and wellbeing needs further elucidation.

The traditional aim to prevent diseases can still be applied to the general older population, including both vital and vulnerable persons. According to GPs, the main topic in the prevention of diseases in the general older population is (apart from the national programs) cardiovascular risk management. A collective approach, consisting of high-risk stratification and treatment, appeared to be possible even at high age. Research on this type of collective approach needs to focus on prevention of diseases, not on detection of disorders which influence independence and wellbeing, because screening does not appear to be the appropriate way to contribute to independence and wellbeing. Future studies should focus on screening to prevent diseases, such as the development of high-risk stratifications in the general older population, especially for cardiovascular risk management but probably also for other programs such as cancer screening and vaccination.
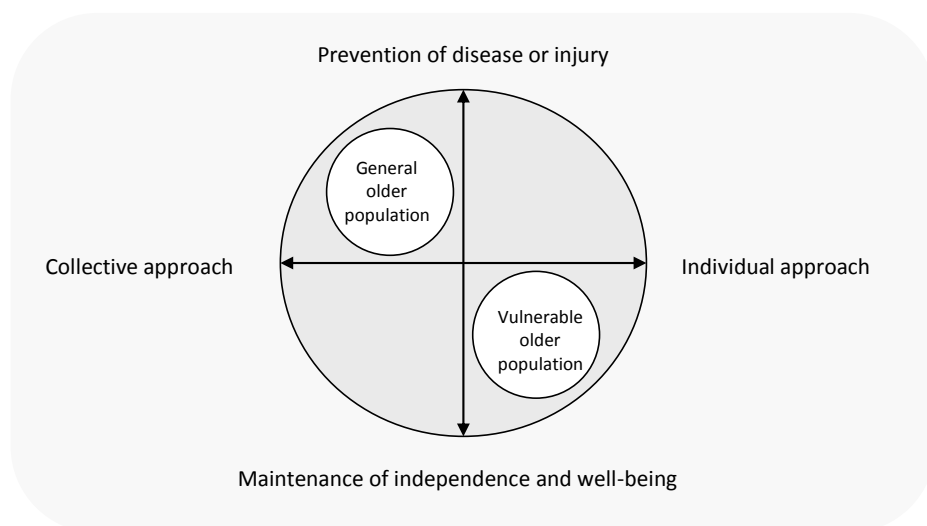

Figure 1. Aims and approaches in preventive strategies.

Finally, the work in this thesis has shown the possibility to develop subgroup specific preventive strategies for older people, stratified according to the two defined aims in prevention. To do justice to the considerable diversity in health status and vitality of older persons, a challenge for future research on the prevention of disease is to incorporate vulnerability into the risk stratification in old age.

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Chapter 9

Summary

SUMMARY

Chapter 1 provides a general introduction and the aims of the work presented in this thesis. The chapter outlines the need for risk stratification in older people, and describes the increase in the aged population as well as the focus on healthy aging in international health policy. According to the Health Council of The Netherlands, prevention (i.e. preventive care) in older people can be applied to contribute to the maintenance of independence and wellbeing by preventing and/or postponing disability and social isolation. However, because prevention traditionally refers to measures taken to prevent disease, injury and death, it is questionable whether prevention can in fact aim at maintenance of independence and wellbeing. Therefore, it is important to explore the possibility of developing strategies in preventive care for older people in order to prevent disease and/or to maintain their independence.

To develop aim-specific preventive care for older people, we not only need instruments to define/select subgroups of older people at risk for disease and/or for loss of independence, but we also require adequate collective or individualized strategies to prevent disease and/or to maintain independence. Therefore, the general aim of this thesis is to study the various strategies (that vary in aim and approach) in prevention for older people to facilitate the development of subgroup-specific, evidence-based guidelines for preventive care for older persons.

To explore the aims and approaches in preventive care, **Chapter 2** starts with an investigation of the views of general practitioners (GPs) on preventive care for older people. Six focus group discussions were held with 37 GPs and were analyzed using the framework analysis method. The main finding was that GPs' perspectives on preventive care are determined by their perception of the level of vitality of their older patients. Preventive care for older people with high levels of vitality may consist of a standardized disease-oriented approach, whereas those who are vulnerable will probably need an individualized approach to prevent functional decline. Based on these perspectives, a conceptual model for preventive care was developed which describes the different perspectives of GPs toward vital and vulnerable older people, focusing on five main dimensions: aim of prevention (disease vs. functional decline), concept of care (disease model vs. functional model), initiator (older persons themselves vs. the GP), target groups (people with request vs. specified risk groups) and content of preventive care (mainly cardiovascular risk management vs. functional decline).

In the aim to prevent functional decline and promote wellbeing, the possibility to identify subgroups of older people needing different types of care is investigated in the

following two chapters. **Chapter 3** describes the predictive value of multimorbidity for the development of disability in the general population of very old people and the role of cognitive impairment in this association. This investigation was part of the Leiden 85-plus Study, an observational prospective cohort study in the general population with 5 years of follow-up. In a total of 594 participants (aged 85+ years), without applying exclusion criteria, disability in activities of daily living (ADL) was measured annually for 5 years with the Groningen Activity Restriction Scale. At baseline, participants with multimorbidity had higher ADL disability scores compared with those without (median 11 vs. 9 ADL points, respectively). Stratified into four groups of cognitive functioning (measured with the MMSE), ADL disability increased over time in all groups, even in those participants without multimorbidity. Multimorbidity predicted accelerated increase in ADL disability in participants with optimal (higher) MMSE scores, but not in participants with lower MMSE scores. Therefore, in very old people the predictive value of multimorbidity for the increase in ADL disability varies with the level of cognitive function; multimorbidity predicts an accelerated increase in ADL disability in very old people with good cognitive function, but not in very old people with cognitive impairment.

GPs seemed to share an implicit concept of vulnerability (Chapter 2). When the vulnerability concepts of GPs appear to be identical, assessment by GPs can be a promising instrument to select older people for specific types of geriatric care. Therefore, **Chapter 4** explores the variation in vulnerability concepts between GPs. The analysis was embedded in the Integrated Systematic Care for Older People (ISCOPE) study, a cluster-randomized controlled trial investigating the effect of pro-active care provided to patients (aged ≥ 75 years) with complex problems. A total of 77 GPs categorized their registered patients (aged ≥ 75 years; n=11,392) into non-vulnerable, possibly vulnerable and vulnerable patients. The personal and practice characteristics of these GPs were collected as well as the characteristics of a sample of 2,828 patients, i.e. socio-demographic characteristics, and characteristics in the functional, somatic, psychological and social domains. The median percentage of vulnerable patients in this age group per GP was 32% (range 2.4-81%). The study showed that GPs share a medical concept of vulnerability because they take somatic and psychological characteristics into account in the vulnerability assessment, but differ in the way that they weigh the functional status.

After investigation of the possibility to select vulnerable older people (Chapter 4), the appropriateness of preventive strategies to contribute to the maintenance of independence and wellbeing is studied in **Chapter 5.** A RAND/UCLA appropriateness method was applied to identify appropriate screening conditions to prevent functional decline in older people, stratified for age and vulnerability. A multidisciplinary panel of 11 experts assessed the appropriateness of screening for 29 conditions mentioned in guide-

lines from four countries, stratified for age (60-74, 75-84 and 85-plus years) and health status (general, vital, and vulnerable). The experts received a literature overview for each condition, including the guidelines and up-to-date literature. After an individual rating round, the expert panel discussed their disagreements and then performed a second individual rating. The expert panel rated screening to be appropriate in 3 of the 29 conditions, indicating that screening was expected to prevent functional decline for these conditions. Screening for insufficient physical activity was considered appropriate for all three age and health groups. Screening for cardiovascular risk factors and smoking was considered appropriate for the general and the vital population aged 60-74 years. When the experts considered the conditions to be inappropriate, this was mainly due to the lack of an adequate screening tool or lack of evidence on effective interventions for positively screened persons. Based on their experience, the expert panel expected some benefit from developing valid applicable tests and effective interventions, especially for the group of vulnerable older people.

To investigate strategies for prevention of disease in the older population, our studies then focused on cardiovascular disease. Therefore, in **Chapter 6** we investigated differences in prognosis between very old people with various levels of prevalent cardiovascular disease, compared to those without manifest cardiovascular disease. The rationale is that, if this classification on the degree of cardiovascular history proves to reveal differences in risk, it will be a simple instrument for GPs to select those persons most in need of maximization of cardiovascular preventive efforts. Again, this study was performed within the Leiden 85-plus Study and was limited to 570 participants with available cardiovascular history. The participants were divided into three groups: no history of cardiovascular disease (CVD), 'minor' CVD (angina pectoris, transient ischemic attack, intermittent claudication and/or heart failure), and 'major' CVD (myocardial infarction, stroke and/or arterial surgery). Investigation of the prognosis took into account not only incident cardiovascular morbidity/mortality, but also functional status. At baseline, 270 (47%) participants had no history of CVD, 128 (22%) minor CVD, and 172 (30%) had major CVD. A history of major CVD almost doubled the risk of a recurrent cardiovascular event or cardiovascular mortality compared to a history of minor CVD; also, this minor CVD group had a 1.6 fold higher risk compared to the no CVD history group. Both minor and major CVD were associated with an accelerated decline in cognitive function and accelerated increase of disability score, being most pronounced in participants with major CVD. These results emphasize the need for physicians and very old patients with a history of major CVD to maximize their cardiovascular preventive efforts. However, in the case of adverse effects or harmful interactions of medication in a very old patient with minor cardiovascular disease, the balance between benefit and harm might change and strict continuation of preventive medication might need to be reconsidered.

Chapter 7 explores ways to optimize the selection of subgroups that will benefit most from preventive cardiovascular medication in old age. This study examines the effect of preventive pravastatin treatment in older people stratified into three groups at risk for cardiovascular disease based on their plasma levels of homocysteine. A post-hoc subanalysis was performed in PROSPER (a large double-blinded randomized placebo-controlled trial) to assess the effect of pravastatin on the risk for coronary heart disease and mortality in older persons, stratified for plasma levels of homocysteine. In the placebo group, participants with high homocysteine (n=588) had a 1.8 higher risk of (non) fatal coronary heart disease compared to those with low homocysteine (n=597). Also, the number needed to treat (NNT) with pravastatin to prevent one (non)fatal coronary heart disease was 15 persons for 3.2 years (the average follow-up period) in the case of high homocysteine, whereas in the low homocysteine group the NNT to prevent an event was 65 persons for the same period. This study suggests that homocysteine may be a promising risk predictor in older people, since high plasma homocysteine not only selects older persons at high risk for (non)fatal coronary heart disease and all-cause mortality, but also identifies those with the highest absolute risk reduction by pravastatin and lowest NNT to prevent (non)fatal coronary heart disease.

Finally, **Chapter 8** presents a general discussion on the main findings of the work in this thesis. The chapter addresses the clinical implications of our results and makes some recommendations for further research. The aim of prevention to maintain independence and wellbeing seems to be appropriate for the vulnerable population. Although a 'gold standard' to stratify for vulnerability in the general older population is lacking, GPs share the same concept of vulnerability for somatic and psychological patient characteristics. However, within the vulnerable older population, there is no evidence (except for physical activity) that a collective screening approach, with a standardized intervention program, will be the most appropriate way to contribute to the maintenance of independence and wellbeing. Moreover, since the majority of vulnerable older people already receive medical care for their chronic disease(s), more benefit can be expected from improving the individual regular care than from a separate collective screening program. The traditional aim to prevent disease can be applied to the general older population, including both vital and vulnerable persons. According to GPs, cardiovascular risk management is the main topic in the prevention of diseases in the general older population, apart from the national programs on cancer screening and vaccination. A collective approach in preventive care, consisting of high-risk stratification and treatment, appeared to be possible for cardiovascular risk management even at high age. Because of the great diversity in the health status and vitality of older people, it will be challenging to incorporate vulnerability in future research into risk stratification for preventive interventions in old age.

Chapter 10

Samenvatting

 SAMENVATTING

Volgens de Gezondheidsraad kan preventie bij ouderen bijdragen aan zelfredzaamheid en welzijn, door het voorkomen of uitstellen van invaliditeit en sociaal isolement. Preventie verwijst echter van oudsher naar maatregelen die worden genomen om ziekte, ongevallen en overlijden te voorkomen. Het is de vraag of preventie ook daadwerkelijk kan bijdragen aan zelfredzaamheid en welzijn. Daarom is het van belang te onderzoeken of preventieve strategieën voor ouderen kunnen worden ontwikkeld ter voorkoming van ziekten en ter behoud van zelfredzaamheid.

Om effectieve preventieve zorg voor ouderen te ontwikkelen, is het noodzakelijk dat subgroepen van ouderen geselecteerd kunnen worden die een verhoogd risico op ziekte of op verlies van zelfredzaamheid hebben. Bovendien moeten er dan collectieve of individuele strategieën beschikbaar zijn om ziekte te voorkomen of om zelfredzaamheid te behouden. Daarom is de doelstelling van dit proefschrift om strategieën in preventieve zorg voor ouderen te onderzoeken die variëren in doel en aanpak, ter bevordering van de ontwikkeling van evidence based richtlijnen voor preventieve zorg voor subgroepen van ouderen.

Hoofdstuk 1 bevat de algemene inleiding en het doel van dit proefschrift. Dit hoofdstuk begint met een beschrijving van de behoefte aan risicostratificatie bij oudere mensen, omdat de groep ouderen zo divers is wat betreft ziekten, functioneren en levensverwachting. Vervolgens wordt de groei van de oudere bevolkingsgroep beschreven en wordt aandacht besteed aan de huidige preventieve zorg voor ouderen in Nederland.

Hoofdstuk 2 beschrijft een onderzoek naar de opvattingen van huisartsen over preventieve zorg voor ouderen. Zes focusgroepbijeenkomsten hebben plaatsgevonden met 37 huisartsen. De discussies in deze focusgroepen zijn geanalyseerd met behulp van de 'framework analysis method'. De belangrijkste bevinding in dit onderzoek is dat de opvattingen van huisartsen over preventieve zorg vooral werden bepaald door hun perceptie van de mate van vitaliteit van hun oudere patiënten. Volgens de huisartsen kon preventieve zorg voor vitale ouderen bestaan uit een gestandaardiseerde ziektespecifieke aanpak ter voorkoming van ziekten. Ouderen die kwetsbaar zijn, hebben een geïndividualiseerde aanpak nodig om functionele achteruitgang te voorkomen. Op basis van deze perspectieven is een conceptueel model voor preventieve zorg ontwikkeld dat de verschillende opvattingen van huisartsen weergeeft over preventieve zorg voor vitale en kwetsbare ouderen. Dit is geordend in vijf dimensies: doel van preventie (voorkomen van ziekte versus functionele achteruitgang), zorgconcept (ziektemodel versus functioneel model), initiatiefnemer (ouderen zelf versus huisarts), doelgroepen

(mensen met een verzoek versus gespecificeerde risicogroepen) en de inhoud van preventieve zorg (vooral cardiovasculair risicomanagement versus voorkomen van functionele achteruitgang).

Voor het gericht aanbieden van preventie om functionele achteruitgang te voorkomen en welzijn te bevorderen is het noodzakelijk om subgroepen van ouderen te kunnen selecteren, voor wie een dergelijk preventief aanbod zinvol is. In de volgende twee hoofdstukken wordt onderzocht of het mogelijk is subgroepen van ouderen hiervoor te selecteren.

Een mogelijke subgroep van ouderen die achteruitgaan en daarom gericht preventieve zorg behoeven, zijn ouderen met multimorbiditeit. **Hoofdstuk 3** beschrijft daarom de voorspellende waarde van multimorbiditeit voor de ontwikkeling van functionele beperkingen in de algemene bevolking van oudste ouderen en de rol van cognitieve stoornissen hierin. Deze studie was onderdeel van de Leiden 85-plus Studie, een observationele prospectieve cohort studie in de algemene bevolking met 5 jaar follow-up. In deze studie golden geen exclusiecriteria. Bij alle 594 85-jarige deelnemers werden met de Groningen Activity Restriction Scale beperkingen in activiteiten van het dagelijks leven (ADL) jaarlijks gemeten gedurende 5 jaar. Op baseline hadden deelnemers met multimorbiditeit hogere ADL scores dan deelnemers zonder multimorbiditeit (mediaan 11 versus 9 ADL punten). De deelnemers werden vervolgens op basis van cognitief functioneren, gemeten met de Mini-Mental State Examination (MMSE), gestratificeerd in vier groepen. In alle groepen namen de beperkingen in ADL in de loop der tijd toe, zowel bij deelnemers met als bij deelnemers zonder multimorbiditeit. Multimorbiditeit voorspelde een versnelde stijging van ADL beperkingen bij deelnemers met goede MMSE scores (MMSE ≥28 punten), maar niet bij deelnemers met lagere MMSE scores. De voorspellende waarde van multimorbiditeit voor de toename in ADL beperkingen is derhalve afhankelijk van de cognitieve functie van oudste ouderen: multimorbiditeit voorspelt versnelde toename van ADL beperkingen bij oudste ouderen met goede cognitieve functie, maar niet bij oudste ouderen met cognitieve stoornissen.

In hoofdstuk 2 leken huisartsen impliciet hetzelfde concept van kwetsbaarheid te hanteren. Als het waar is dat huisartsen identieke kwetsbaarheidconcepten gebruiken, kan het huisartsenoordeel over kwetsbaarheid een veelbelovend instrument zijn om ouderen te selecteren die meer complexe zorg behoeven. Daarom is in **hoofdstuk 4** de variatie in kwetsbaarheidbeoordelingen tussen de huisartsen onderzocht. De analyse werd ingebed in de Integrated Systematic Care for Older People (ISCOPE) study, een cluster-gerandomiseerde gecontroleerde trial naar het effect van pro-actieve zorgplanning bij patiënten met complexe problemen van 75 jaar en ouder. Zevenenzeventig

huisartsen hebben hun ingeschreven 75-plus patiënten (n=11.392) onderverdeeld in niet-kwetsbare, mogelijk kwetsbare en kwetsbare patiënten. Van deze huisartsen werden zowel persoonskenmerken als praktijkkenmerken verzameld. Bovendien waren van een steekproef van 2828 patiënten de patiëntkenmerken verzameld: socio-demografische kenmerken en kenmerken in de functionele, somatische, psychologische en sociale domeinen. Het mediane percentage kwetsbare patiënten per huisarts was 32% en vari-eerde van 2,4 tot 81%. De studie toonde aan dat huisartsen eenzelfde medische invul-ling gaven aan het begrip kwetsbaarheid, omdat zij de somatische en psychologische kenmerken uniform betrokken in het kwetsbaarheidoordeel. De huisartsen verschilden echter in de manier waarop ze de functionele status en eenzaamheid van patiënten in het kwetsbaarheidoordeel lieten meewegen.

Na onderzoek van de mogelijkheden om kwetsbare ouderen te selecteren (hoofdstuk 4), wordt in **hoofdstuk 5** onderzocht welke screening evidence-based bijdraagt aan het bevorderen van zelfredzaamheid van ouderen. Voor dit onderzoek is gebruik ge-maakt van de 'RAND/UCLA appropriateness method'. Dit is een methode waarmee een multidisciplinair panel op basis van literatuur en expert-opinion evidence kan wegen. Elf experts hebben op basis van literatuur en screeningsrichtlijnen uit vier landen de evidence voor screening voor 29 onderwerpen gewogen. Voor elk onderwerp werd voor drie verschillende leeftijdsgroepen (60-74 jaar, 75-84 jaar, 85-plus) en drie gezond-heidsniveaus (algemeen, vitaal, kwetsbaar) het nut van screening gescoord, eerst in een individuele scoreronde, gevolgd door een paneldiscussie en een tweede individuele ronde. Het panel oordeelde dat voor drie van de 29 onderwerpen screening nuttig was: screening op onvoldoende fysieke activiteit was zinvol voor alle leeftijdsgroepen en alle gezondheidsniveaus. Screening op cardiovasculaire risicofactoren en roken was zinvol voor ouderen in de algemene populatie en de vitale ouderen van 60-74 jaar. Het ontbreken van een adequaat screeningsinstrument en het ontbreken van evidence over de effectiviteit van interventies waren de meest voorkomende redenen om screening als 'niet nuttig' te kwalificeren. Ontwikkeling van valide screeningsinstrumenten en/of effectieve interventies kan in de toekomst bijdragen aan het bevorderen van zelfred-zaamheid, met name van kwetsbare ouderen.

De volgende hoofdstukken betreffen strategieën voor de preventie van ziekten bij ouderen en richten zich specifiek op hart- en vaatziekten. Het doel van **hoofdstuk 6** is om de verschillen in prognose tussen zeer oude mensen met milde en ernstige cardiovasculaire voorgeschiedenis te onderzoeken en deze groepen te vergelijken met degenen zonder manifeste hart- en vaatziekten in de voorgeschiedenis. Immers, als de ernst van de cardiovasculaire geschiedenis het risico op hart- en vaatziekten voorspelt, dan is de cardiovasculaire voorgeschiedenis een eenvoudig instrument voor huisartsen

om ouderen te selecteren die het meest baat hebben bij specifieke preventieve interventies. Deelnemers van de Leiden 85-plus Studie werden ingedeeld in drie groepen: geen cardiovasculaire voorgeschiedenis (47%), milde cardiovasculaire voorgeschiedenis (angina pectoris, TIA, claudicatio intermittens en/of hartfalen) (22%) en ernstige cardiovasculaire voorgeschiedenis (myocardinfarct, beroerte en/of arteriële chirurgie) (30%). In vergelijking met een milde cardiovasculaire voorgeschiedenis werd door een ernstige cardiovasculaire voorgeschiedenis het risico op het optreden van een cardiovasculaire ziekte of cardiovasculaire mortaliteit vrijwel verdubbeld. Bovendien had de groep met een milde cardiovasculaire voorgeschiedenis een 1,6 maal hoger risico op het optreden van een cardiovasculaire ziekte dan de groep zonder cardiovasculaire voorgeschiedenis. Zowel een milde als een ernstige cardiovasculaire voorgeschiedenis bleken een versnelde achteruitgang van cognitief en lichamelijk functioneren te voospellen, alweer het meest uitgesproken in de groep met een ernstige cardiovasculaire voorgeschiedenis. Deze resultaten tonen het belang om bij ouderen met een ernstige cardiovasculaire voorgeschiedenis de cardiovasculaire preventie te maximaliseren. Wanneer echter bij oude patiënten met een milde cardiovasculaire voorgeschiedenis bijwerkingen of schadelijke interacties van medicatie optreden, kan de balans tussen voor- en nadeel van strikte voortzetting van preventieve medicatie anders uitslaan en dient de noodzaak van preventieve interventies te worden heroverwogen.

Het volgende hoofdstuk onderzoekt de mogelijkheden om subgroepen te definiëren die het meest baat hebben bij preventieve cardiovasculaire medicatie op hoge leeftijd. **Hoofdstuk 7** beschrijft een studie naar de verschillen in effect van preventieve behandeling met pravastatine op cardiovasculair risico bij oudere mensen afhankelijk van hun homocysteïne plasmaspiegel. In PROSPER, een grote, dubbelblind gerandomiseerde placebo-gecontroleerde studie, werd een post-hoc subanalyse uitgevoerd. In de niet behandelde placebogroep hadden deelnemers met een hoog homocysteïne (n=588) een 1,8 maal hoger risico op al dan niet fatale coronaire hartziekten dan deelnemers met een laag homocysteïne (n=597). Deze studie toonde aan dat 15 mensen met hoog homocysteïne behandeld moeten worden (number needed to treat) met pravastatine gedurende 3,2 jaar (de gemiddelde follow-up tijd van de studie) om een al dan niet fatale coronaire hartziekte te voorkomen. Voor de groep met laag homocysteïne moeten 65 personen gedurende 3,2 jaar behandeld moeten worden om ditzelfde resultaat te behalen. Deze studie laat zien dat homocysteïne een veelbelovende nieuwe risicovoorspeller is voor coronaire hartziekten bij ouderen; met een homocysteïnebepaling kunnen ouderen worden geselecteerd die niet alleen een hoog risico op al dan niet fatale coronaire hartziekten hebben en algemene sterfte, maar ook degenen bij wie de grootste reductie in het absolute risico met pravastatine behaald kan worden. Voor de toekomst betekent dit dat dat door het bepalen van het homocysteïne de groep oude-

ren met de laagste 'number needed to treat' kan worden geselecteerd, ter voorkoming van al dan niet fatale coronaire hartziekten.

Hoofdstuk 8 bevat de belangrijkste bevindingen, de algemene discussie met aansluitend de klinische implicaties van de bevindingen en aanwijzingen voor verder onderzoek. Het bevorderen van zelfredzaamheid lijkt een geschikt doel voor preventie voor de groep kwetsbare ouderen. Een gouden standaard om de algemene oudere bevolking in te delen naar kwetsbaarheid ontbreekt echter. Huisartsen blijken evenwel eenzelfde medisch concept van kwetsbaarheid te hanteren, waarin zij de somatische en psychologische kenmerken van hun oudere patiënten laten meewegen. Er is echter geen bewijs dat het zinvol is om deze groep kwetsbare ouderen te gaan screenen op allerhande onderwerpen (met uitzondering van screening op onvoldoende fysieke activiteit). Een collectief screeningsaanbod met een gestandaardiseerd interventieprogramma lijkt derhalve niet de juiste manier om bij te dragen aan zelfredzaamheid van kwetsbare ouderen. Aangezien de meeste kwetsbare ouderen al vanwege hun chronische ziekte(n) reguliere zorg ontvangen, lijkt voor deze groep het verbeteren van de individuele zorg meer winst te kunnen opleveren dan een afzonderlijk collectief screeningsprogramma.

Het traditionele doel van preventie om ziekten te voorkomen, blijft een zinvol doel voor preventieve programma's voor ouderen in het algemeen. Huisartsen denken bij preventie van ziekten voor de algemene groep ouderen naast de nationale programma's voor kankerscreening en vaccinatie vooral aan cardiovasculair risicomanagement. Risicostratificatie in het kader van cardiovasculair risicomanagement is bij ouderen mogelijk, zelfs op hoge leeftijd. Bovendien is met behulp van risicostratificatie een groep ouderen te selecteren met het hoogste risico op nieuwe coronaire hartziekten en is in die groep ook de grootste absolute risicoreductie te bereiken met preventieve medicamenteuze behandeling. Gezien het feit dat lang niet alle ouderen met een indicatie voor preventieve cardiovasculaire medicatie deze medicatie ook daadwerkelijk slikken, is nader onderzoek noodzakelijk om te bepalen welke ouderen het meeste baat hebben bij preventieve medicamenteuze behandeling. Bovendien is het vanwege de grote diversiteit in de gezondheidstoestand en vitaliteit van ouderen belangrijk om in toekomstig onderzoek naar effecten van preventieve interventies bij ouderen de mate van kwetsbaarheid op te nemen in de risicostratificatie.

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Curriculum Vitae

CURRICULUM VITAE

Yvonne Drewes was born on 20 September 1969 in Utrecht, the Netherlands. She passed her gymnasium-β exam at Hermann Wesselink College in Amstelveen in 1987. At VU University Amsterdam she finished medical school (1987-1996) and graduated from law school (1988-1994). Next, she worked as a medical advisor for the Health Care Insurance Board. In 1997, she started to work at the VU University Medical Center Amsterdam as a medical and legal advisor in the department for Medical Affairs and followed her training for specialist in community medicine at the Netherlands School of Public Health in Utrecht (1997-2000). She was head of the department for Medical Affairs in the VU University Medical Center Amsterdam from 2003 till 2006. In 2007, she started with her PhD research project described in this thesis at the department of Public Health and Primary Care of the Leiden University Medical Center. Besides her thesis, she worked on a randomized controlled trial on functional physical training of older persons with complex health problems with TNO Healthy Living Leiden and participated in a multi-disciplinary evaluation study on patients' self-determination, together with colleagues attached to Leiden Law School. In 2013 she started working for the Royal Dutch Medical Association (KNMG) in Utrecht as a legal and medical advisor.

Yvonne is married to Jan-Kees Jol. They have two daughters, Marianne (2001) and Simone (2003) and a son, Bart (2006).