HEALTHY AGEING

HEALTH PROMOTION FOR PEOPLE WITH FRAILTY AND CHRONIC CONDITIONS

Xuxi Zhang

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Healthy Ageing

Health Promotion for People with Frailty and Chronic Conditions

Gezond ouder worden

gezondheidsbevordering voor kwetsbare mensen en mensen met chronische aandoeningen

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Chapter 3

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Chapter 4

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Chapter 1

General Introduction

1.1 BACKGROUND

According to the data from World Population Prospects 2019, the proportion of the population aged over 65 years will increase from 9% in 2019 to 16% in 2050, and the number of people aged over 80 years is projected to triple, from 143 million in 2019 to 426 million in 2050.[1] Globally, the older population grows bigger due to the increasing longevity and decreasing fertility.[1, 2] People may experience multiple challenges from the physical, psychological and social perspectives when they grow older. People aged over 65 years are presumed to live almost half of their remaining lives with a limiting long-term physical or mental condition.[3] Therefore, alongside with the extension of life quantity among the increasingly older population, it is important to find out novel ways to improve people's health and quality of life during the extended years.[2, 4]

Healthy Ageing

The concept of healthy ageing was first put forward by Robetr Havighurst in 1961, by which he meant that older adults prefer to stay actively involved in the activities that they were engaged in in their earlier life.[5] With the increase of older people worldwide, healthy ageing attracts more and more attention in recent decades. In 2002, the World Health Organization (WHO) defined healthy ageing as "the process of developing and maintaining the functional ability that enables wellbeing in older age".[6] WHO general director Margaret Chan, at that time, emphasized that "healthy ageing is more than just the absence of disease; the maintenance of functional ability has the highest importance".[7] The requirement of healthy ageing is not the absence of disease or infirmity because there will inevitably occur relatively more chronic and acute conditions for older adults with the increasing longevity.[6] The challenge of healthy ageing is to manage and live well with the conditions, and make their influence on people's wellbeing less.[6]

Healthy ageing is a life-long process, and life choices or interventions at different points during the life course may determine the functional trajectory of each individual.[7, 8] The most favorable outcome is to maintain intrinsic capacity, and live in functional independence within your own surroundings until the end of life.[7, 8]

In order to realize healthy ageing, the society should take actions against risk factors for (future) disability and dependency throughout the life cycle. The risk factors related to healthy ageing could be divided into four categories: (1) "non-modifiable" risk factors, such as genetics, gender and ethnic background, (2) "distal" risk factors, such as economic background, socio-cultural determinants, education and air pollution, (3) "intermediate" risk factors, such as health behaviors, living and working conditions and access to healthcare, and (4) "proximal" risk factors, such as frailty, chronic conditions (e.g. hypertension and diabetes) and cognitive impairments.[8, 9] Since the "proximal" risk factors are most closely related to health conditions and disability, actions targeted at these factors are often considered to be the priority in promotion of healthy ageing.[8] Therefore, in this thesis, we studied health

promotion with regard to people with frailty and chronic conditions in order to provide insights and directions in developing health promotion to support healthy ageing of older people.

Frailty

With the demographic process of ageing all over the world, frailty is increasingly recognized as one of the most serious public health challenges today.[10] According to Clegg et al. (2013) and Hoogendijk et al. (2019), frailty develops as a consequence of decline in functioning across multiple physiological systems, accompanied by an increased vulnerability to stressors.[11, 12] Figure 1.1.1 shows the concept of frailty diagrammatically with the comparison of the change in health state after a small stress event in life between a fit person and a frail person; the frail person (the red line in Figure 1.1.1) may experience a larger deterioration in functional abilities due to the vulnerability.[12]

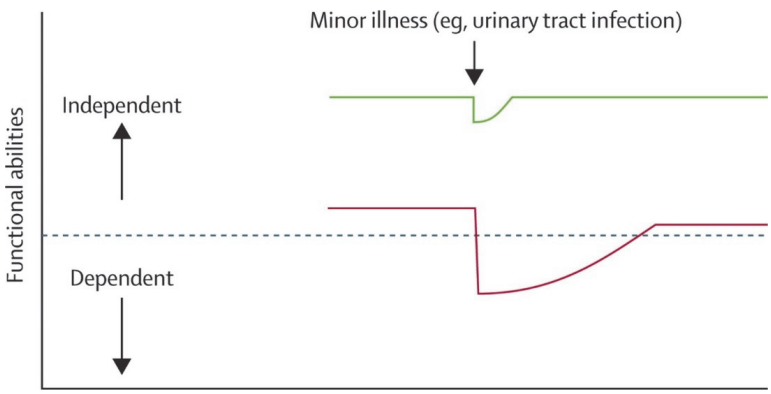

Figure 1.1.1 Vulnerability of frail elderly people to a sudden change in health status after a minor illness*

*The **green line** represents a fit elderly individual who, after a minor stressor event such as an infection, has a small deterioration in function and then returns to homoeostasis. The **red line** represents a frail elderly individual who, after a similar stressor event, undergoes a larger deterioration, which may manifest as functional dependency, and who does not return to baseline homoeostasis. The **horizontal dashed line** represents the cutoff between dependent and independent.*

* Reprinted from The Lancet, 381(9868), Clegg, A., Young, J., Iliffe, S., Rikkert, M. O., & Rockwood, K., Frailty in elderly people, 752–762, Copyright (2013), with permission from Elsevier.

Despite discussions regarding the conceptualization of frailty over the past decades, three important factors of frailty remaining consistent.[11, 13] Firstly, frailty is a multidimensional concept with physical, psychological and social factors playing a role in its development.[11, 13] Secondly, frailty is an extreme consequence of the normal ageing process although its prevalence increases with age.[11] Thirdly, frailty is dynamic which means the level of frailty of an individual could change in either direction over time.[11, 14]

It has been shown that frail people may have a higher risk of various negative outcomes such as falls[15], disability[16], long-term care[17], hospitalization[16] and mortality[18]. To identify frail people has been proposed as a step for better management and control of frailty.[10] However,

there is no global standard assessment measure for frailty.[11] Although many assessment tools to measure frailty have been developed in the past decades, there are relatively few validation studies for many frailty measures.[10, 11]

Furthermore, researchers, health care professionals and policymakers increasingly acknowledge the multidimensional nature of frailty.[17, 19] However, many measures only cover the physical domain, such as the frailty phenotype[16] and the frailty indexes[20, 21] , but not the psychological and social domains.[11] The Tilburg Frailty Indicator (TFI) is one of the multidimensional frailty measures. The TFI considers frailty from a bio-psycho-social framework and includes 15 items addressing 3 domains: the physical, psychological and social domains.[22] Pialoux et al. (2012) proposed that the TFI is an appropriate measure for screening frailty in primary health care settings.[23]

Besides the frailty measures, relatively few studies examine frailty from the multidimensional perspective. Some studies related to frailty are focused on physical frailty only,[12, 24, 25] however studies on the psychological and social frailty are also needed to provide insight regarding the determinants of and the management of frailty.

Chronic conditions

Hajat and Stein (2018) reported that around 16–57% of adults in developed countries suffer from one or more chronic conditions.[26] With the increasing proportion of older adults in the population and increasing proportion of younger adults with chronic conditions who will live to advanced ages worldwide, it is anticipated that the burden of chronic conditions will increase in the near future.[26, 27] Chronic conditions may have negative effects on the quality of life of affected individuals[28]. Chronic conditions can be associated with not only premature mortality[29] but also a negative impact on economic and social effects in families[30], communities and societies in general.[31]

Successful self-management of chronic conditions could help citizens handle their life with independence to some extent despite their chronic condition and to feel 'healthy' even in the presence of certain limitations.[32] Moreover, within the context of the healthcare and welfare systems that experience challenges, the ability of adults with a chronic condition to take care of themselves for as long as possible has become increasingly important.[32]

Diabetes is a chronic condition with significant morbidity and mortality which may result in blindness, kidney failure, heart attacks, stroke and lower limb amputation due to the complications of diabetes.[33] The worldwide prevalence of diabetes among adults is 451 million (age 18-99 years) in 2017 and is anticipated to rise to 693 million by 2045.[34] Among all the patients with diabetes, around 90–95% have type 2 diabetes (T2DM) which "encompasses individuals who have insulin resistance and usually have relative (rather than absolute) insulin deficiency"(P. S83).[33]

The main characteristic of T2DM is hyperglycemia, and the degree and duration of hyperglycemia are associated with the microvascular complications, such as retinopathy, nephropathy, and neuropathy.[35, 36] Diabetic retinopathy (DR) is an important risk factor of preventable blindness,[37] and more than 60% of those with T2DM will develop DR.[38] The modifiable risk factors of T2DM and its complications, such as hyperglycemia, hypertension, hyperlipidemia, obesity, and lifestyle, have been identified by previous studies.[38-40]

On-going changes in lifestyle including diet, exercise, medication management and monitoring clinical and metabolic parameters may be effective in better management and control of T2DM as well as its complications.[41, 42] However, these changes in lifestyle are difficult for the adults with T2DM due to the requirement of strong self-management or self-regulation skills.[41, 43]

Peer support, a kind of ongoing support from nonprofessionals, may contribute to effectively providing ongoing self-management support and help adults with T2DM change and sustain the key behaviors.[41, 44, 45] A guide developed by the Victorian Department of Human Services in Australia proposed seven types of peer support: (1) Have a chat, (2) Support groups, (3) Internet and email peer support, (4) Peer-led groups or events, (5) Individual peer coaches, (6) Telephone-based peer support, and (7) Community workers and service provider-led groups.[46]

Mindfulness has recently been explored as a potential concept that could help people deal with the challenges of chronic conditions.[47, 48] Mindfulness-based stress reduction interventions could enable participants with chronic conditions to better cope with symptoms and better achieve overall well-being, quality of life and health outcomes.[49] Previous studies also reported that mindfulness interventions may have positive effect on better self-management of diabetes[50] as well as chronic low back pain[51].

However, there are relatively few studies regarding the effectiveness of interventions among adults with chronic conditions to promote self-management. More studies on interventions to enable adults with T2DM as well as other chronic conditions to enhance self-management of chronic conditions are needed.

Public Health Framework

In order to contribute to effective ways to manage frailty and chronic conditions so as to promote healthy ageing and enable people to perceive greater wellbeing in their own lives, the Public Health Framework[52] may be applied to study health promotion for people with frailty and chronic conditions. We use it in this thesis. The public health framework involves four steps: (1) defining the problem (surveillance), (2) identifying the cause or risk and protective factors for the problem, (3) determining how to prevent or control the problem, (4) implementing effective interventions and evaluating their effect (see Figure 1.1.2).[52, 53]

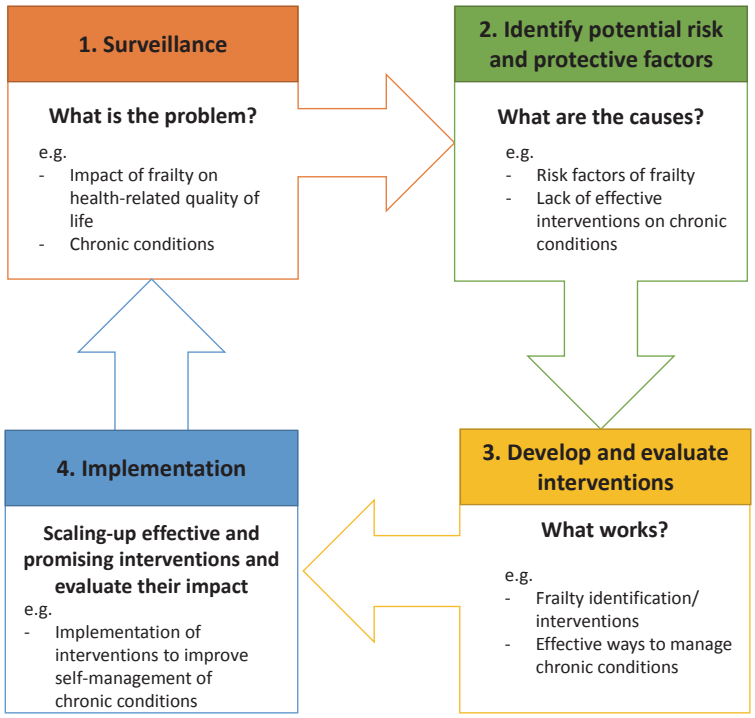

Figure 1.1.2 Public health framework: the steps of public health approach*

*This is an adaptation of an original work "The public health approach. Geneva: World Health Organization (WHO); 2010. Licence: CC BY-NC-SA 3.0 IGO". This adaptation was not created by WHO. WHO is not responsible for the content or accuracy of this adaptation. The original edition shall be the binding and authentic edition.

1.2 THIS THESIS

Research questions

In this thesis, the aim is to investigate frailty and chronic conditions from the public health perspective. The study questions are:

Health promotion for people with frailty

1. What are the associations between physical, psychological and social frailty and health-related quality of life (HRQoL) among community-dwelling older adults? **(Step 1 of Public Health Framework)**
2. What are the longitudinal associations between physical activity (PA) and frailty as well as the association between a 12-month change in physical activity and frailty among community-dwelling older adults? **(Step 2 of Public Health Framework)**
3. What are the reliability and validity of the Tilburg Frailty Indicator (TFI) in 5 European countries? **(Step 3 of Public Health Framework)**
4. How does the Urban Health Centres Europe (UHCE) approach perform in terms of specific process components? **(Step 3 of Public Health Framework)**

Health promotion for people with chronic conditions

5. What are the effects of peer support on glycemic control for adults with type 2 diabetes (T2DM) and the characteristics of effective peer support? **(Step 3 of Public Health Framework)**
6. What are the effects of interventions targeting modifiable risk factors on diabetic retinopathy (DR) for adults with T2DM and the characteristics of effective interventions? **(Step 3 of Public Health Framework)**
7. Could the Social Engagement Framework for Addressing the Chronic-disease-challenge (SEFAC) intervention be effective to promote the self-management of chronic conditions and a healthy lifestyle? **(Step 4 of Public Health Framework)**

Outline of this thesis

Table 1.2.1 provides an overview of the six studies presented in this thesis. The research focus of these studies can be divided into two topics related to health promotion of healthy ageing. ***Part 1*** of this thesis consists of studies on health promotion for people with frailty. In **Chapter 2**, the associations between physical, psychological and social frailty and HRQoL among community-dwelling older people are studied. In **Chapter 3**, the longitudinal associations between frequency of moderate physical activity (PA) and overall, physical, psychological and social frailty among community-dwelling older people are studied. In addition, the associations between a 12-month change in frequency of moderate PA and overall, physical, psychological and social frailty are studied. In **Chapter 4**, the internal consistency, convergent and divergent validity and concurrent validity of the TFI within community-dwelling older people in Spain, Greece, Croatia, the Netherlands and the United Kingdom (UK) are studied. In **Chapter 5**, specific process components of a coordinated preventive care approach on fall risk, appropriate medication use, loneliness and frailty (UHCE approach, more details are described in the next paragraph) aimed to promote healthy ageing among older adults are studied to evaluate how the approach is implemented, which persons are reached and what their experience is with this approach. ***Part 2*** of this thesis consists of studies on health promotion for people with chronic conditions. In **Chapter 6**, the effects of different kinds of peer support on glycemic control, in terms of providers, types of support, intervention duration and effect duration, are studied to find out how to achieve better effects of peer support on glycemic control among adults with T2DM. In **Chapter 7**, the effects of different interventions targeting modifiable risk factors on DR are studied to find out how to perform better interventions to prevent and control DR among adults with T2DM. In **Chapter 8**, the evaluation design of SEFAC project aimed to empower citizens at risk of or with T2DM and/or cardiovascular disease to self-manage their chronic conditions through the SEFAC intervention is described. Finally, in **Chapter 9**, an overall discussion, including recommendations and implications for future research, policy and practice, is provided.

Table 1.2.1 Overview of the studies presented in the thesis

Chapter	Study design	Study/data	Sample	Population in analysis	Research focus
Part 1 Health promotion for people with frailty					
2	Cross-sectional	UHCE	Community-dwellers aged ≥70 years	N= 2,167	The associations between physical, psychological and social frailty and health-related quality of life
3	Longitudinal	UHCE	Community-dwellers aged ≥70 years	N= 1,735	The longitudinal associations between frequency of moderate PA and overall, physical, psychological and social frailty; the association between a 12-month change in frequency of moderate PA and frailty
4	Cross-sectional	UHCE	Community-dwellers aged ≥70 years	N= 2,250	The reliability and validity of the Tilburg Frailty Indicator in 5 European countries
5	Mixed-methods study	UHCE	Community-dwellers aged ≥70 years and professionals participating in UHCE approach	N= 986 & 23	Evaluation of UHCE approach regarding process components: context, reach, dose delivered and received, satisfaction and experience
Part 2 Health promotion for people with chronic conditions					
6	Meta-analysis	PubMed, Web of science, ScienceDirect	Adults with T2DM	20 RCTs (N = 4,494)	To study the effects of different kinds of peer support on glycemic control, in terms of providers, types of support, intervention duration and effect duration
7	Meta-analysis	PubMed, Embase and ScienceDirect	Adults with T2DM	22 RCTs (N= 22,511)	To study the effects of different interventions targeting modifiable risk factors on DR
8	Design paper	SEFAC	Community-dwellers at risk of or with T2DM and/or CVD aged ≥50 years	N/A	Evaluation design of the SEFAC project aimed to empower citizens to self-manage their chronic conditions through the SEFAC intervention

Abbreviations: UHCE = the Urban Health Centres Europe project; PA = physical activity; DR = diabetic retinopathy; SEFAC =the Social Engagement Framework for Addressing the Chronic-disease-challenge project; RCTs= randomized control trials; T2DM = type 2 diabetes; CVD = cardiovascular disease

1.3 STUDIES AND DATA

The UHCE project

The Urban Health Centres Europe (UHCE) project aimed to promote the healthy ageing of older adults using integrated care pathways regarding the adherence to medication, prevention of falls and frailty and loneliness.[54, 55] Integrated care pathways were implemented in community settings at study sites in five European countries (Spain, Greece, Croatia, the Netherlands and the UK). At each study site, older adults over age 70, who lived independently and were expected to be able to participate in the study for at least 6 months were invited to participate. A total of 2325 participants were recruited between May 2015 and June 2017, of which 1215 received integrated care pathways (intervention) and 1110 were enrolled in the control group. At the 12-month follow-up, 986 persons in the intervention group (81.2%) completed the questionnaire and 858 persons in the control group (77.3%) completed the questionnaire. Participants in the intervention group received care in accordance with the UHCE approach which comprised three stages: risk assessment, shared-decision making and referral to care pathways aimed at reducing fall risk, inappropriate medication use, loneliness and frailty by specific interventions.[55] Data were obtained from self-reported questionnaires at baseline and at 12 months of follow-up.

The SEFAC project

The Social Engagement Framework for Addressing the Chronic-disease-challenge (SEFAC) project was set up to respond to the call of the Third EU Health Programme (2014–2020; PJ-04-2016: Support to Member States and stakeholders to address the chronic disease challenge; http://sefacproject.eu). The aim of the SEFAC project is to empower citizens ≥50 years of age at risk of or with T2DM and/or cardiovascular disease (CVD) to self-manage their chronic conditions through the SEFAC intervention, which combines elements of mindfulness, social engagement as well as information and communication technology (ICT) support. A prospective cohort study with a 6-month pre-post design is being conducted in four European countries: Croatia, Italy, the Netherlands and the United Kingdom.[56]

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PART

I

Health promotion for people with frailty

2

Chapter 2

Association between physical, psychological and social frailty and health-related quality of life among older people

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ABSTRACT

Background Studies on the association between frailty and health-related quality of life (HRQoL) are scarce and show contradictory results. This study aimed to evaluate the association between physical, psychological and social frailty and HRQoL among community-dwelling older people.

Methods A cross-sectional study was performed with baseline data collected in 2015 from the Urban Health Centers Europe (UHCE) project in five European countries, the United Kingdom, Greece, Croatia, The Netherlands and Spain. A total of 2325 participants were included in the baseline measurements of the UHCE project; 2167 participants (mean age = 79.7; SD = 5.6) were included in the analyses after excluding participants with missing data. The Tilburg Frailty Indicator measured overall frailty as well as physical, psychological and social frailty. The 12-Item Short-Form Health Survey (SF-12) was used to measured physical and mental HRQoL.

Results Regarding physical HRQoL, a large difference (d = 1.29) between physically and not physically frail participants was observed. Regarding mental HRQoL, a large difference (d = 1.20) between psychologically and not psychologically frail participants was observed. In the full model with all three domains of frailty and the covariates to explain physical HRQoL, physical ($p < .001$) and social frailty ($p < .001$) remained significant. In the full model to explain mental HRQoL, all three domains of frailty remained significant($p < .001$).

Conclusions Physical frailty had the strongest association with physical HRQoL, and psychological frailty had the strongest association with mental HRQoL. The associations between social frailty and both physical and mental HRQoL remain significant when controlling physical and psychological frailty.

KEYWORDS Frailty; Physical, psychological and social frailty; Health-related quality of life; Community-dwelling older people

INTRODUCTION

Health-related quality of life (HRQoL) is a multidimensional construct that specifically focuses on health-related aspects of well-being. It includes elements about physical and mental functioning, as well as a person's subjective appraisal of their effect on daily life and social functioning.[1] For frail people, HRQoL may be restricted. Frailty is a multidimensional syndrome characterized by the loss of reserves including energy, physical ability, cognition and health and is highly prevalent with increasing age.[2-4] As the proportion of the European citizens aged 65 years and older is expected to further rise from 18% in 2013 to 27% in 2040[5], more people will suffer from frailty in the near future.[4, 6] Therefore, the literatures of studies regarding the HRQoL of frail people increase.[6, 7]

However, studies on the association between frailty and HRQoL are still scarce and show contradictory results.[8] Several cross-sectional studies using generic or specific instruments for measuring HRQoL reported that frailty is associated with poorer HRQoL among older people.[3, 4, 8-12] Where some studies found that poor endurance and energy had the strongest effect[3, 4, 12] , another study observed slowness and poor endurance to have the strongest effect on poorer HRQoL.[9]

Because of its multidimensional nature, it has been suggested to consider frailty broadly from a physical, psychological and social perspective when examining the association between frailty and HRQoL.[10] However, there is yet no consensus on the associations between the three domains of frailty and HRQoL. Some studies suggest that psychological and social frailty had a significant *negative* effect on HRQoL.[10, 13, 14] For example, a cross-sectional study in The Netherlands found that psychological and social frailty significantly contributed to the ability of physical frailty to predict HRQoL.[10] However, one longitudinal study found no significant effect of social frailty on HRQoL.[15] Thus, more studies on this topic are needed to clarify the association between the three domains of frailty and HRQoL.

Frailty is a common problem among older people, and study to explore the association between frailty and HRQoL could provide insight needed for further development of effective interventions to improve HRQoL.[16] It might provide professionals with starting points to optimize the (timely) choice of interventions and to establish tailored support for frail people at risk for suboptimal HRQoL. Understanding HRQoL in frail people could finally help policy makers develop more precise policies for healthy aging.

The aim of this present study is to evaluate the association between physical, psychological and social frailty and HRQoL among community-dwelling older people in five European countries. We hypothesize that overall frailty is associated with poorer physical and mental HRQoL. Also, we hypothesize that physical frailty is associated with poorer physical HRQoL, psychological frailty with poorer mental HRQoL and social frailty with poorer physical and mental HRQoL.

METHODS

Participants

This study was performed within the framework of the Urban Health Centres Europe (UHCE) project. The project was funded by the European Commission Executive Agency for Health and Consumers and aimed to promote healthy life styles, health and HRQoL of older people in the United Kingdom, Greece, Croatia, The Netherlands and Spain.[5] The recruitment procedure has been described in detail elsewhere[5, 17]. In short, the pre-post controlled intervention study measured 2325 participants at baseline and 12 months later in 2015 and 2017. Persons were invited when they were at least 70 years, lived independently and were expected to be able to participate in the study for at least 6 months. Persons were excluded if they lacked the basic knowledge of local language or if they were not expected to be able to make an informed decision regarding participation in the project. Ethical committee procedures have been followed in all cities and approval has been provided. Written informed consent was obtained from all participants. The study was registered as ISRCTN52788952.

This study is a cross-sectional study using baseline data from UHCE project. Supplementary Figure S1 presents the population of the present analysis. Participants with missing data on HRQoL (n = 127), frailty and the three domains of frailty (n = 27) and on age or sex (n = 4) were excluded. Hence, 2167 participants were included in the analyses of this study.

Procedure

The data collection was done by means of a questionnaire. A trained researcher conducted a face-to-face self-reported semi-structured interview at the home of the participant in United Kingdom, Croatia, the Netherlands and Spain. In Greece, the interview was taken at community centers and the Municipal health Center. More details could be found elsewhere.[5, 17] The interview included, among others, the 12-Item Short-Form Health Survey (SF-12)[18] and the Tilburg Frailty Indicator (TFI)[19, 20].

Frailty

The TFI is a questionnaire based on a multidimensional approach to measure frailty and was made and validated for use in primary care. The TFI consists of 15 self-reported questions covering three domains: physical (eight items, score range 0-8), psychological (4; 0-4) and social frailty (3; 0-3).[19, 20] Participants with total score of at least 5 were diagnosed as being frail.[19] The cut points for physical, psychological and social frailty were 3, 2 and 2 respectively.[19, 21]

HRQoL

The SF-12 is a widely used patient-reported survey for measuring general HRQoL.[18] The SF-12 consists of 12 questions covering eight health domains, including general health, mental health, vitality, social functioning, role limitation due to physical health problems, role limitation due to emotional problems, bodily pain limiting usual activities, and physical functioning. The eight domains of SF-12 can be summarized in the Physical Component

Summary (PCS) and Mental Component Summary (MCS), both ranging from 0 (lowest) to 100 (highest level of health).[18, 22]

Covariates

Various socio-demographic characteristics were assessed at baseline and incorporated as covariates[23, 24], including age (in years), sex and country. Education level concerned the highest level of education the participant completed and was categorized according to the 2011 International Standard Classification of Education (ISCED) into primary or less (ISCED 0-1), secondary or equivalent (ISCED 2-5) and tertiary or higher (ISCED 6-8). Living situation was categorized into living with others ('with partner, no child', 'with partner and children', 'without partner, with children' or 'in a household shared with others') or not living with others. With respect to life style, three aspects were measured. Firstly, three items of the AUDIT-C measured high-risk alcohol use on a scale ranging from 0 (lowest risk) to 12 (highest risk)[25]. A score of 4 or more in men and a score of 3 or more in women indicate hazardous drinking or active alcohol use disorders.[25] Secondly, one item on exercise assessed the frequency of a person being engaged in activities that require low or moderate energy (once a week or less versus more than once a week). Thirdly, one item on smoking assessed whether a person smoked. Finally, multi-morbidity was defined as having at least two of 14 common chronic conditions[26], including heart attack, hypertension, diabetes, stroke, high blood cholesterol, asthma, arthritis, osteoporosis, chronic lung disease, cancer or malignant tumor, stomach or duodenal ulcer, Parkinson's disease, cataract and hip or femoral fracture.[27]

Statistical analyses

In order to examine mean differences in PCS and MCS scores between frail and not frail groups, effect sizes were estimated by dividing the difference in mean scores between subgroups by the largest SD. Cohen's effect sizes (d) were used for the interpretation of relevant differences: $0.20 \leq d < 0.50$ was considered a small difference; $0.50 \leq d < 0.80$ was considered a moderate difference; $d \geq 0.80$ was considered a large difference.[28]

To control for the cluster effect of countries we performed multilevel linear regression models as well as multivariate linear regression models, but found similar results (data not shown). Hence, we chose three multivariate linear regression models to investigate the independent contribution of frailty on HRQoL. PCS and MCS scores were included as the dependent variable. The first model regarded only frailty, physical, psychological or social frailty as determinant (*crude model*). The second model additionally included the covariates as determinants (*adjusted model*). To explore the contribution of the three domains of frailty on HRQoL, the third model included all three domains of frailty and the covariates as determinants (*full model*). Regression diagnostics included tests for linearity between the determinants and dependent variables and tests for normality of residuals with kernel density plots. Variance inflation factors were adopted for tests of multicollinearity. No violation of basic assumptions for regression and no multicollinearity problems were found.

Finally, we assessed interactions between frailty as well as three domains of frailty and socio-

demographic variables including age, sex, country, education level and live situation in the association between frailty as well as three domains of frailty and HRQoL. UNIANOVA was adopted for interaction analyses. After applying Boneferroni correction for multiple testing (*P* = 0.05/40 = 0.001), no statistically significant interaction was found. All *P*-values of the interaction analyses are presented in Supplementary Table S2.

Analyses were performed with SPSS version 23.0 (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp). A *P*-value < 0.05 was considered as statistically significant.

RESULTS

Participants characteristics

Table 1 summarizes the general characteristics of the study population. The mean age of participants was 79.7 (SD = 5.6) years and 60.6% were female. Among the 2167 participants, 1195 (55.1%) were frail. Compared with participants who were not frail, frail participants were older ($p < 0.001$), more often female ($p < 0.001$), more often had a secondary or lower education level ($p < 0.001$), more often lived alone ($p < 0.001$), less often were at risk for alcohol use ($p < 0.001$), less often did exercise more than once a week ($p < 0.001$) and more often had multi-morbidity ($p < 0.001$).

Supplementary Table S1 shows the general characteristics distributed by domain of frailty. Among the 2167 participants, 1173 (54.1%) were physically frail, 843 (38.9%) were psychologically frail and 629 (29.0%) were socially frail.

Compared to persons included in the analysis (Supplementary Figure S1; n = 2167), persons excluded due to missing information (n = 158) were more often smoker ($p = 0.01$) and had lower MCS scores ($p = 0.001$). No other significant differences were found between these two groups.

Frailty and HRQoL

Table 2 presents the comparison of HRQoL scores among different frailty groups. Compared with participants who were not frail, frail participants had significantly lower scores for both PCS ($p < 0.001$) and MCS ($p < 0.001$) and the differences in physical HRQoL (d = 1.10) as well as mental HRQoL (d = 0.98) were large.

Participants who were physically, psychologically or socially frail had significantly lower scores for both PCS and MCS ($p < 0.001$).

With respect to physical HRQoL, a large difference (d = 1.29) between physically and not physically frail participants was observed, a small difference (d = 0.47) between psychologically and not psychologically frail participants and a small difference (d = 0.39) between socially and not socially frail participants.

Regarding mental HRQoL, a large difference (d = 1.20) between psychologically and not psychologically frail participants was observed and moderate differences between physically and not physically frail participants (d = 0.69) and between socially and not socially frail participants (d = 0.54).

Table 1 Characteristics of study population (n=2167)

Items	Total (n=2167) Mean±SD N(%)	Frailty		*P-value*
		Yes (n=1195) Mean±SD N(%)	No (n=972) Mean±SD N(%)	
Age	79.7±5.6	80.4±5.8	78.7±5.3	**<0.001**
Sex				**<0.001**
Male	854(39.4)	363(30.4)	491(50.5)	
Female	1313(60.6)	832(69.6)	481(49.5)	
Country				**<0.001**
The United Kingdom	537(24.8)	248(20.8)	289(29.7)	
Greece	327(15.1)	214(17.9)	113(11.6)	
Croatia	476(22.0)	356(29.8)	120(12.3)	
The Netherlands	331(15.3)	133(11.1)	198(20.4)	
Spain	496(22.9)	244(20.4)	252(26.9)	
Education level[a]				**<0.001**
Primary or less	586(27.3)	352(29.8)	234(24.3)	
Secondary or equivalent	1361(63.5)	746(63.2)	615(63.9)	
Tertiary or higher	196(9.1)	83(7.0)	113(11.7)	
Living situation[a]				**<0.001**
Living with others	1341(62.0)	641(53.8)	700(72.1)	
Living alone	822(38.0)	551(46.2)	271(27.9)	
Life style-Alcohol[a]				**<0.001**
No alcohol risk	1520(73.6)	903(80.2)	617(65.8)	
Alcohol risk	544(26.4)	223(19.8)	321(34.2)	
Life style-Exercise[a]				**<0.001**
Once a week or less	609(28.3)	484(40.9)	125(12.9)	
More than once a week	1544(71.7)	700(59.1)	844(87.1)	
Life style-Smoking[a]				0.467
Not smoking	2005(92.7)	1102(92.4)	903(93.2)	
Smoking	157(7.3)	91(7.6)	66(6.8)	
Multi-morbidity[a]				**<0.001**
No	195(9.0)	50(4.2)	145(14.9)	
Yes	1971(91.0)	1145(95.8)	826(85.1)	

Note: Significant *P*-values in bold.

[a]Missing items: Education level=24; Living situation=4; Life style-Alcohol=103; Life style-Exercise=14; Life style-Smoking=5; Multi-morbidity=1

SD, standard deviation

Table 2 Frailty and HRQoL scores (n=2167)

Items	HRQOL Scores Mean±SD	
	PCS	MCS
Total (n=2167)	41.77±12.07	50.27±10.70
Frailty		
Yes (n=1195)	36.62±11.84	46.10±11.22
No (n=972)	48.11±8.93	55.41±7.27
Effect Size[b]	1.10[a]	0.98[a]
Physical Frailty		
Yes (n=1173)	35.81±11.40	47.12±11.45
No (n=994)	48.81±8.54	54.00±8.33
Effect Size[b]	1.29[a]	0.69[a]
Psychological Frailty		
Yes (n=843)	38.39±12.39	43.32±10.69
No (n=1324)	43.93±11.35	54.70±8.03
Effect Size[b]	0.47[a]	1.20[a]
Social Frailty		
Yes (n=629)	38.50±12.13	46.25±11.04
No (n=1538)	43.11±11.79	51.92±10.11
Effect Size [b]	0.39[a]	0.54[a]

Abbreviations: PCS, Physical Component Suammary summarized by the SF-12; MCS, Mental Component Suammary summarized by the SF-12.

[a] $p<0.001$, P-values are based on Independent T test for frail and not frail groups.

[b] Cohen's effect size (d) for differences in HRQOL between frail and not frail groups. $0.20 \leq d < 0.50$ is considered a small difference; $0.50 \leq d < 0.80$ a moderate difference; $d \geq 0.80$ a large difference.

SD, standard deviation

Multivariate linear regression models

Table 3 presents the multivariate linear regression models for frailty and HRQoL. Being frail was significantly associated with lower HRQoL scores ($p < 0.001$). The associations were partly explained by the covariates. With respect to physical HRQoL, living in Greece (versus Spain), having completed secondary education or equivalent (versus Tertiary education or higher) and smoking were not significantly associated. The amount of variance explained by the crude model was 23.2% and was 38.2% in the adjusted model. Regarding mental HRQoL, living in the Netherlands (versus Spain), having completed secondary education or equivalent (versus Tertiary education or higher), high-risk alcohol use, smoking and multi-morbidity were not significantly associated. The amount of variance explained by the crude model was 19.3% and was 27.2% in the adjusted model.

Table 3 Multivariate linear regression model (frailty and HRQoL)

Items	PCS		MCS	
	Crude Model	Adjusted Model	Crude Model	Adjusted Model
Frailty				
Yes vs. No	**-11.69[c]**	**-8.49[c]**	**-9.47[c]**	**-7.30[c]**
Age		**-0.17[c]**		**0.13[b]**
Sex				
Female vs. male		**-1.55[b]**		**-1.18[a]**
Country				
The United Kingdom versus Spain		**-5.42[c]**		**-1.87[a]**
Greece vs. Spain		-0.12		**-1.86[a]**
Croatia vs. Spain		**-4.58[c]**		**-6.35[c]**
The Netherlands vs. Spain		**-5.43[c]**		0.19
Education level				
Primary or less vs. tertiary or higher		**-1.95[a]**		**-2.50[b]**
Secondary or equivalent vs. tertiary or higher		0.34		-1.35
Living situation				
Living alone vs. living with others		**1.22[a]**		**0.98[a]**
Life style				
Alcohol risk vs. no alcohol risk		**1.34[b]**		0.71
Exercise once a week or less vs. more than once a week		**-7.50[c]**		**-3.71[c]**
Smoking vs. not smoking		0.97		-0.25
Multi-morbidity				
Yes vs. No		**-4.64[c]**		0.09
Adjusted R^2, %	23.2	38.2	19.3	27.2

Note: Abbreviations: PCS, Physical Component Suammary summarized by the SF-12; MCS, Mental Component Suammary summarized by the SF-12.
The Crude Model is the unadjusted model with frailty as determinant.
The Adjusted Model is the adjusted model with frailty and the covariates as determinants.
[a] $p<0.05$, [b] $p<0.01$, [c] $p<0.001$, significant P-values in bold.

Table 4 presents the multivariate linear regression models for the domains of frailty and HRQoL. Physical frailty had the strongest association with physical HRQoL. In the adjusted models, the mean PCS score of physically frail participants was 9.94 lower than that of not physically frail participants ($p < 0.001$). The mean PCS score of psychologically frail participants was 3.21 lower than that of not psychologically frail participants ($p < 0.001$) and the mean PCS score of socially frail participants 2.54 lower than that of not socially frail participants ($p < 0.001$). Among the three adjusted models, the amount of variance explained was largest for physical frailty (42.6%).

Table 4 Multivariate linear regression model (Three domains of frailty and HRQoL)

Items	PCS							MCS						
	Crude Model	Adjusted Model	Crude Model	Adjusted Model	Crude Model	Adjusted Model	Full Model	Crude Model	Adjusted Model	Crude Model	Adjusted Model	Crude Model	Adjusted Model	Full Model
Frailty (Yes vs. No)														
Physical frailty	**-13.06**[c]	**-9.94**[c]					**-9.71**[c]	**-7.04**[c]	**-4.08**[c]					**-1.50**[c]
Psychological frailty			**-5.65**[c]	**-3.21**[c]			-0.47			**-11.46**[c]	**-9.58**[c]			**-8.59**[c]
Social frailty					**-4.86**[c]	**-2.54**[c]	**-1.37**[a]					**-5.73**[c]	**-5.87**[c]	**-3.76**[c]
Age		**-0.15**[c]		**-0.26**[c]		**-0.26**[c]	**-0.15**[c]		**0.10**[a]		0.07		0.07	**0.09**[a]
Sex														
Female vs. male		**-1.33**[b]		**-2.31**[c]		**-2.68**[c]	**-1.33**[b]		**-1.59**[b]		**-1.11**[a]		**-2.20**[c]	**-1.07**[a]
Country														
The United Kingdom vs. Spain		**-5.00**[c]		**-5.01**[c]		**-4.78**[c]	**-5.05**[c]		-1.40		**-2.06**[b]		-1.36	**-2.05**[b]
Greece vs. Spain		-0.54		-0.87		-1.19	-0.24		**-2.70**[c]		-0.92		**-2.16**[b]	-0.37
Croatia vs. Spain		**-4.09**[c]		**-5.32**[c]		**-5.58**[c]	**-3.88**[c]		**-6.74**[c]		**-5.80**[c]		**-6.77**[c]	**-5.25**[c]
The Netherlands vs. Spain		**-5.11**[c]		**-4.78**[c]		**-4.19**[c]	**-5.01**[c]		0.77		0.00		**1.59**[a]	0.35
Education level														
Primary or less vs. tertiary or higher		-1.29		**-2.27**[a]		**-2.60**[b]	-1.22		**-2.56**[b]		**-1.91**[a]		**-2.96**[b]	**-1.71**[a]
Secondary or equivalent vs. tertiary or higher		0.63		0.40		0.11	0.60		-1.30		-0.87		**-1.66**[a]	-0.98
Living situation														
Living alone vs. living with others		-0.29		-0.04		**1.30**[a]	0.36		-0.16		-0.33		**2.82**[c]	**1.46**[b]
Life style														
Alcohol risk vs. no alcohol risk		**1.00**[a]		**1.82**[b]		**1.98**[c]	**0.99**[a]		0.86		0.75		**1.24**[a]	0.64

Table 4 Multivariate linear regression model (Three domains of frailty and HRQoL) (Continued)

Items	PCS							MCS						
	Crude Model	Adjusted Model	Crude Model	Adjusted Model	Crude Model	Adjusted Model	Full Model	Crude Model	Adjusted Model	Crude Model	Adjusted Model	Crude Model	Adjusted Model	Full Model
Exercise once a week or less vs. more than once a week		**-7.07**[c]		**-9.12**[c]		**-9.48**[c]	**-6.96**[c]		**-4.50**[c]		**-3.98**[c]		**-5.17**[c]	**-3.51**[c]
Smoking vs. not smoking		1.23		0.33		0.39	1.16		-0.37		-1.05		-0.84	-0.99
Multi-morbidity														
Yes vs. No		**-4.58**[c]		**-6.23**[c]		**-6.24**[c]	**-4.46**[c]		-0.72		-0.77		-0.96	-0.21
Adjusted R^2, %	29.0	42.4	5.1	30.2	3.3	29.4	42.6	10.7	21.3	27.0	34.7	5.8	22.7	36.8

Note: Abbreviations: PCS, Physical Component Suammary summarized by the SF-12; MCS, Mental Component Suammary summarized by the SF-12.
The Crude Model is the unadjusted model with one domain of frailty (physical, psychological or social frailty) as determinant.
The Adjusted Model is the adjusted model with one domain of frailty (physical, psychological or social frailty) and the covariates as determinants.
The Full Model is the adjusted model with physical, psychological and social frailty and the covariates as determinants.
[a] $p<0.05$, [b] $p<0.01$, [c] $p<0.001$, significant P-values in bold.

In the full model, only physical ($p < 0.001$) and social frailty ($p < 0.05$) remained significant. Living in Greece (vs. Spain), having completed primary education or less/secondary education or equivalent (vs. tertiary education or higher), living alone and smoking were not significantly associated with the PCS score.

Psychological frailty had the strongest association with mental HRQoL. In the adjusted models, the mean MCS score of physically frail participants was 4.08 lower than that of not physically frail participants ($p < 0.001$). For psychologically frailty this figure amounted to 9.58 ($p < 0.001$) and for social frailty to 5.87 ($p < 0.001$). Among the three adjusted models, the amount of variance explained was largest for psychological frailty (36.8%).

In the full model, physical, psychological and social frailty each remained significant ($p < 0.001$). Living in Greece or the Netherlands (versus Spain), having completed secondary education or equivalent (versus Tertiary education or higher), high-risk alcohol use, smoking and multimorbidity were not significantly associated with the MCS score.

DISCUSSION

The aim of this study was to explore the association between physical, psychological and social frailty versus HRQoL among community-dwelling older people in five Europe countries. Consistent with previous studies, our results show that frail people have a poorer physical and mental HRQoL than not frail people.[3, 4, 8, 16, 29] This also holds for physical, psychological and social frailty separately.[29, 30]

Physical frailty

Our findings confirm that physical frailty has the strongest association with physical HRQoL. Also, the addition of physical frailty contributed to the ability of psychological frailty to explain mental HRQoL. A study in the Netherlands also found that the prevalence rate of physical frailty among depressed participants was higher than that of non-depressed participants, and physical frailty was associated with more severe depressive symptoms, which might because physical frailty may result in more severe mental disorders due to its association with chronic somatic disease and functional limitations.[31] However, studies on this topic are scarce, and studies on physical frailty and mental HRQoL are needed to confirm our findings.

Psychological frailty

Psychological frailty had the strongest association with mental HRQoL. However, psychological frailty did not contribute to the ability of physical frailty to explain physical HRQoL. The latter is in contrast to earlier studies[10, 15], which may be explained by the fact that previous studies adopted the WHOQOL-BREF instead of SF-12 to measure HRQoL and did not classify HRQoL into physical and mental HRQoL. More studies are still needed to clarify these findings.

Social frailty

Furthermore, this research found that social frailty contributed to the ability of physical frailty to explain physical HRQoL and to the ability of psychological frailty to explain mental HRQoL, which was not reported by previous studies. Some studies reported that poor social contact and support could influence HRQoL negatively.[10, 32] A qualitative study for older people in the Netherlands found that 'when participants' health was poor, there was a shift from health to social contacts as the most important aspect to quality of life'. [33] Other studies proved that increasing social contact and social support were associated with better health behavior and HRQoL.[34, 35] In frail people, where physical interventions are not practical, increasing social contact or social support to reduce social frailty could be a proper choice to positively influence HRQoL.[36] A previous study suggested that early identification and intervention can enable frail people to maintain control over their HRQoL for longer.[21] Our findings suggest that considering social frailty is important to improve both physical and mental HRQoL. They implicate that health professionals and policy makers should pay more attention to social frailty among older persons and could consider improving social support or social contact to improve HRQoL of older people in Europe in the future.

Our study has some limitations. Although we made use of two validated questionnaires, cultural differences in the interpretation of questions might still have caused some variation between countries. In addition, the SF-12 has been validated in UK, Greece, Croatia, The Netherlands and Spain[37], but the TFI has not been validated in all the five countries yet. Currently, TFI is validated in the Netherlands[19] and Spain[38]. Nevertheless, our results indicate that the TFI is a suitable screening instrument for assessing overall frailty as well as the three domains of frailty in order to maintain or improve HRQoL. Secondly, we adopted cut points of frailty and its three domains instead of exact scores to explore the association between frailty and HRQoL which might cause information loss. However, we performed analyses on the association between exact frailty scores and HRQoL (see Supplementary Table S3-4). The only difference was that the score of social frailty was negatively associated with PCS score in the full model but no longer significant. All other significant results remained significant in the same direction. Thirdly, relatively healthy participants may have enrolled to the study which potentially caused selection bias. However, due to the inclusion of the rich data of 2327 participants at baseline, we do not expect that this limitation changed our findings. Finally, the cross-sectional design of this study did not allow to establish the causal relationship between frailty and HRQoL. Our results support the need for further research on evaluating the effects of frailty as well as the three domains of frailty on HRQoL.

CONCLUSION

Physical, psychological and social frailty each has a negative association with both physical and mental HRQoL. The addition of physical frailty contributed to the ability of psychological frailty to explain mental HRQoL. The associations between social frailty and both physical and mental HRQoL remain significant when controlling for physical and psychological frailty, which implicates the importance of improving social support or social contact to improve HRQoL. In summary, our results confirm the importance of considering the three domains of frailty to improve physical and mental HRQoL.

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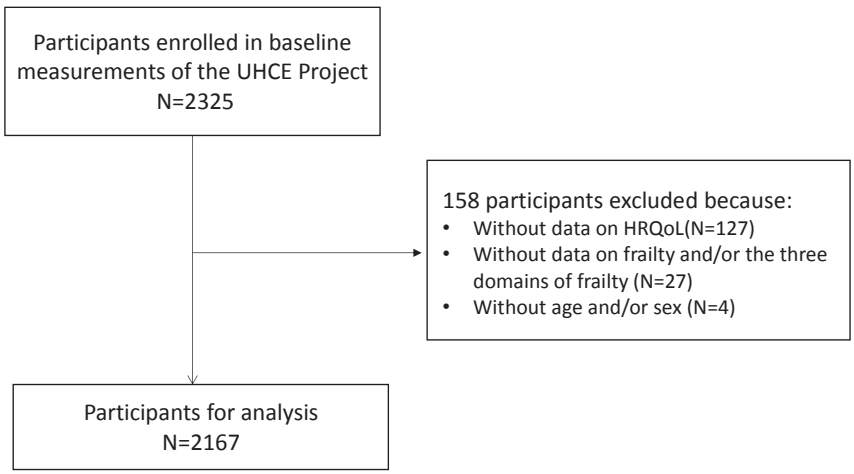

Supplementary Figure S1 Population of analyses

Supplementary Table S1 Participants characteristics, stratified for three domains of frailty

Items	Physical Frailty			Psychological Frailty			Social Frailty		
	Yes (N=1173)	No (N=994)	*P-value*	Yes (N=843)	No (N=1324)	*P-value*	Yes (N=629)	No (N=1538)	*P-value*
Age	80.5±5.6	78.7±5.4	**<0.001**	79.6±5.7	79.7±5.5	0.624	80.8±5.8	79.2±5.5	**<0.001**
Sex			**<0.001**			**<0.001**			**<0.001**
Male	377(32.1)	477(48.0)		263(31.2)	591(44.6)		170(27.0)	684(44.5)	
Female	796(67.9)	517(52.0)		580(68.8)	733(55.4)		459(73.0)	854(55.5)	
Country			**<0.001**			**<0.001**			**<0.001**
UK	248(21.1)	289(29.1)		136(16.1)	401(30.3)		145(23.1)	392(25.5)	
Greece	187(15.9)	140(14.1)		191(22.7)	136(10.3)		105(16.7)	222(14.4)	
Croatia	358(30.5)	118(11.9)		264(31.3)	212(16.0)		167(26.6)	309(20.1)	
NL	137(11.7)	194(19.5)		73(8.7)	258(19.5)		113(18.0)	218(14.2)	
Spain	243(20.7)	253(25.5)		179(21.2)	317(23.9)		99(15.7)	397(25.8)	
Education[a]			**<0.001**			**<0.001**			0.335
Primary or less	343(29.5)	243(24.8)		267(32.1)	319(24.3)		175(28.2)	411(27.0)	
Secondary or equivalent	744(64.0)	617(62.9)		513(61.7)	848(64.7)		398(64.1)	963(63.3)	
Tertiary or higher	75(6.5)	121(12.3)		52(6.3)	144(11.0)		48(7.7)	148(9.7)	
Living situation[a]			**0.047**			0.414			**<0.001**
Live with others	703(60.1)	638(64.2)		531(63.1)	810(61.3)		144(23.0)	1197(77.9)	
Live alone	467(39.9)	355(35.8)		311(36.9)	511(38.7)		483(77.0)	339(22.1)	
Lifestyle-Alcohol[a]			**<0.001**			**<0.001**			**0.016**
No alcohol risk	897(80.7)	623(65.4)		637(79.8)	883(69.7)		463(77.3)	1057(72.2)	
Alcohol risk	214(19.3)	330(34.6)		161(20.2)	383(30.3)		136(22.7)	408(27.8)	
Lifestyle-Exercise[a]			**<0.001**			**<0.001**			**<0.001**
Once a week or less	481(41.4)	128(12.9)		331(39.6)	278(21.1)		225(36.1)	384(25.1)	
More than once a week	681(58.6)	863(87.1)		504(60.4)	1040(78.9)		399(63.9)	1145(74.9)	
Lifestyle-Smoking[a]			0.409			0.389			0.644
Not smoking	1081(92.3)	924(93.2)		785(93.3)	1220(92.4)		584(93.1)	1421(92.6)	
Smoking	90(7.7)	67(6.8)		56(6.7)	101(7.6)		43(6.9)	114(7.4)	
Multi-morbidity[a]			**<0.001**			**0.001**			**<0.001**
No	54(4.6)	141(14.2)		54(6.4)	141(10.7)		31(4.9)	164(10.7)	
Yes	1119(95.4)	852(85.8)		789(93.6)	1182(89.3)		597(95.1)	1374(89.3)	

Note: Data presented as mean±SD or number (percentage); Significant P-values in bold.

[a]Missing items: Education level=24; Living situation=4; Life style-Alcohol=103; Life style-Exercise=14; Life style-Smoking=5; Multi-morbidity=1

SD, standard deviation

Supplementary Table S2 *P*-values for interactions between socio-demographic variables and frailty as well as three domains on PCS and MCS

Items	PCS	MCS
	***P*-value**	***P*-value**
frailty*country	0.068	0.001
frailty*age	0.144	0.148
frailty*sex	0.658	0.658
frailty*live situation	0.089	0.074
frailty*educational level	0.686	0.568
physical frailty*country	0.237	0.002
physical frailty*age	0.186	0.456
physical frailty*sex	0.587	0.610
physical frailty*live situation	0.056	0.217
physical frailty*educational level	0.483	0.154
psychological frailty*country	0.137	0.051
psychological frailty*age	0.312	0.553
psychological frailty*sex	0.005	0.088
psychological frailty*live situation	0.334	0.423
psychological frailty*educational level	0.142	0.214
social frailty*country	0.830	0.313
social frailty*age	0.666	0.518
social frailty*sex	0.548	0.244
social frailty*live situation	0.601	0.118
social frailty*educational level	0.789	0.338

Note: Abbreviations: PCS, Physical Component Suammary summarized by the SF-12; MCS, Mental Component Suammary summarized by the SF-12.

UNIANOVA was adopted for interaction analyses with correction of covariates including age, sex, country, education level and live situation.

After applying Boneferroni correction for multiple testing (P=0.05/40=0.001), no statistically significant interaction was found.

Supplementary Table S3 Multivariate linear regression model (Frailty score and HRQoL)

Items	PCS		MCS	
	Crude Model	Adjusted Model	Crude Model	Adjusted Model
Frailty score	**-2.13[c]**	**-1.77[c]**	**-1.86[c]**	**-1.66[c]**
Age		**-0.15[c]**		**0.16[c]**
Sex				
Female vs. male		**-1.35[b]**		**-0.91[a]**
Country				
The United Kingdom vs. Spain		**-5.46[c]**		**-1.96[b]**
Greece vs. Spain		1.09		-0.61
Croatia vs. Spain		**-2.70[c]**		**-4.48[c]**
The Netherlands vs. Spain		**-5.41[c]**		0.13
Education level				
Primary or less vs. tertiary or higher		-0.59		-1.18
Secondary or equivalent vs. tertiary or higher		0.83		-0.88
Living situation				
Living alone vs. living with others		**2.01[c]**		**1.80[c]**
Life style				
Alcohol risk vs. no alcohol risk		**0.94[a]**		0.28
Exercise once a week or less vs. More than once a week		**-6.15[c]**		**-2.28[c]**
Smoking vs. not smoking		0.84		-0.33
Multi-morbidity				
Yes vs. no		**-4.30[c]**		0.54
Adjusted R^2, %	31.5	43.2	30.4	34.5

Note: Abbreviations: PCS, Physical Component Suammary summarized by the SF-12; MCS, Mental Component Suammary summarized by the SF-12.
The Crude Model is the unadjusted model with frailty as determinant.
The Adjusted Model is the adjusted model with frailty and the covariates as determinants.
[a] $p<0.05$, [b] $p<0.01$, [c] $p<0.001$, significant P-values in bold

Supplementary Table S4 Multivariate linear regression model (Score of three domains of frailty and HRQoL)

Items	PCS							MCS						
	Crude Model	Adjusted Model	Crude Model	Adjusted Model	Crude Model	Adjusted Model	Full Model	Crude Model	Adjusted Model	Crude Model	Adjusted Model	Crude Model	Adjusted Model	Full Model
Frailty (Yes vs. No)														
Physical frailty	**-3.49**[c]	**-2.94**[c]					**-2.99**[c]	**-2.12**[c]	**-1.46**[c]					**-0.47**[c]
Psychological frailty			**-2.94**[c]	**-1.78**[c]			0.30			**-5.58**[c]	**-4.83**[c]			**-4.09**[c]
Social frailty					**-2.77**[c]	**-1.56**[c]	-0.18					**-3.45**[c]	**-4.16**[c]	**-2.26**[c]
Age		**-0.10**[a]		**-0.26**[c]		**-0.26**[c]	**-0.10**[a]		**0.13**[b]		0.07		0.07	**0.11**[b]
Sex														
Female vs. male		**-1.26**[b]		**-2.20**[c]		**-2.64**[c]	**-1.31**[b]		**-1.44**[b]		**-0.90**[a]		**-2.10**[c]	**-0.85**[a]
Country														
The United Kingdom vs. Spain		**-5.38**[c]		**-5.03**[c]		**-4.80**[c]	**-5.35**[c]		**-1.61**[a]		**-2.05**[b]		-1.42	**-2.10**[b]
Greece vs. Spain		-0.14		-0.50		-0.98	-0.23		**-2.41**[b]		-0.12		-1.46	0.56
Croatia vs. Spain		**-2.44**[b]		**-5.30**[c]		**-5.41**[c]	**-2.42**[b]		**-5.77**[c]		**-5.88**[c]		**-6.21**[c]	**-4.88**[c]
The Netherlands vs. Spain		**-5.74**[c]		**-4.84**[c]		**-4.23**[c]	**-5.67**[c]		0.40		-0.07		**1.57**[a]	0.17
Education level														
Primary or less vs. tertiary or higher		-0.71		**-2.07**[a]		**-2.41**[b]	-0.75		**-2.16**[a]		-1.48		**-2.42**[b]	-1.03
Secondary or equivalent vs. tertiary or higher		0.67		0.47		0.25	0.64		-1.24		-0.72		-1.32	-0.67
Living situation														
Living alone vs. living with others		-0.08		0.02		**1.90**[b]	0.14		-0.09		-0.15		**4.88**[c]	**2.50**[c]
Life style														
Alcohol risk vs. no alcohol risk		0.67		**1.78**[b]		**1.95**[c]	0.68		0.61		0.69		**1.16**[a]	0.50
Exercise once a week or less vs. more than once a week		**-5.59**[c]		**-8.90**[c]		**-9.38**[c]	**-5.61**[c]		**-3.55**[c]		**-3.51**[c]		**-4.83**[c]	**-2.77**[c]

Supplementary Table S4 Multivariate linear regression model (Score of three domains of frailty and HRQoL) (Continued)

Items	PCS						MCS							
	Crude Model	Adjusted Model	Crude Model	Adjusted Model	Crude Model	Adjusted Model	Crude Model	Adjusted Model	Crude Model	Adjusted Model	Crude Model	Adjusted Model	Crude Model	Adjusted Model
Smoking vs. not smoking		1.20		0.40		0.46	1.22		-0.33		-0.85		-0.69	-0.70
Multi-morbidity														
Yes vs. No		**-3.75**[c]		**-6.14**[c]		**-6.31**[c]	**-3.74**[c]		-0.14		-0.57		-1.04	-0.03
Adjusted R^2, %	38.4	48.0	6.7	30.9	4.1	29.5	48.0	18.0	24.4	30.9	37.9	8.2	24.9	40.4

Note: Abbreviations: PCS, Physical Component Suammary summarized by the SF-12; MCS, Mental Component Suammary summarized by the SF-12.
The Crude Model is the unadjusted model with one domain of frailty (physical, psychological or social frailty) as determinant.
The Adjusted Model is the adjusted model with one domain of frailty (physical, psychological or social frailty) and the covariates as determinants.
The Full Model is the adjusted model with physical, psychological and social frailty and the covariates as determinants.
[a] $p<0.05$, [b] $p<0.01$, [c] $p<0.001$, significant P-values in bold

3

Chapter 3

Longitudinal association between physical activity and frailty among community-dwelling older adults

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ABSTRACT

Objectives To examine the longitudinal association between frequency of moderate physical activity (PA) and overall, physical, psychological and social frailty among community-dwelling older adults older than 70 years. Second, we assessed the association between a 12-month change in frequency of moderate PA and frailty.

Design Longitudinal cohort study.

Setting Community settings in Spain, Greece, Croatia, the Netherlands and the United Kingdom.

Participants 1735 participants (61.1% female; mean age = 79.6 years; SD = 5.5 years).

Measurements The frequency of self-reported moderate PA was measured and classified into two categories: 'regular frequency' and 'low frequency'. The 12-month change in frequency of moderate PA between baseline and follow-up was classified into four categories: 'continued regular frequency', 'decreased frequency', 'continued low frequency' and 'increased frequency'. The 15-item Tilburg Frailty Indicator assessed overall, physical, psychological and social frailty.

Results Participants who undertook moderate PA with a regular frequency at baseline were less frail at 12-month follow-up than participants with a low frequency. Participants who undertook moderate PA with a continued regular frequency were least frail at baseline and at 12-month follow-up. After controlling for baseline frailty and covariates, compared with participants with a continued regular frequency, participants with a decreased frequency were significantly more overall (B = 1.31; 95%CI = 0.99,1.63), physically (B = 0.80; 95%CI = 0.58,1.03), psychologically (B = 0.43; 95%CI = 0.30,0.56) and socially frail (B = 0.14; 95%CI = 0.04,0.23) at 12-month follow-up; participants with a continued low frequency were significantly more overall (B = 1.16; 95%CI = 0.84,1.49), physically (B = 0.73; 95%CI = 0.51,0.96), psychologically (B = 0.42; 95%CI = 0.29,0.55) and socially frail (B = 0.13; 95%CI = 0.04,0.23) at 12-month follow-up; the 12-month follow-up frailty level of participants who undertook moderate PA with an increased frequency was similar to those with a continued regular frequency.

Conclusions Maintaining a regular frequency of PA as well as increasing to a regular frequency of PA are associated with maintaining or improving overall, physical, psychological and social frailty among European community-dwelling older adults older than 70 years.

KEYWORDS Physical activity; Frailty; Physical frailty; Psychological frailty; Social frailty

INTRODUCTION

Frailty is a multidimensional concept characterized by the loss of reserves including energy, physical ability, cognition and health. The prevalence of frailty strongly increases with age.[1] According to the 2018 Ageing Report of the European Commission, the percentage of European citizens aged 65 years or older will rise from 19% in 2018 to 29% in 2070.[2] This increase is predominantly caused by the percentage of citizens aged 80 years and older. [2, 3] Hence, it is anticipated that frailty will pose a larger public health problem in the near future.[3-5]

Maintaining a healthy lifestyle in older age is associated with a lower level of frailty.[3, 6-8] However, studies on the association between physical activity (PA) and frailty among older adults show contradictory results. Some studies[4, 9-11] suggest that regular PA may delay the onset of frailty and reduce its severity, but others[12] found that PA was not associated with a decreased risk for frailty among older adults. Second, most of the longitudinal studies on PA and frailty examine baseline PA only in relation to changes in frailty[11, 13], and evidence on the association between change in PA and frailty is quite limited. Additionally, most studies[7, 11, 14, 15] on PA and frailty have been conducted in adults aged 50 to 70 years, and evidence on the longitudinal association between PA and frailty in adults older than 70 years is relatively scarce.

Due to the multidimensional nature of frailty, it has been suggested that the physical, psychological and social dimensions of frailty should be considered.[16] However, most previous studies on PA and frailty have focused on physical frailty only[4, 9, 11-13], and to date there has been little research into psychological and social frailty.

Therefore, the aim of our study was to examine the longitudinal association between frequency of moderate PA and overall, physical, psychological and social frailty among community-dwelling older adults older than 70 years. Second, we assessed the association between a 12-month change in frequency of moderate PA and frailty.

METHODS

Participants

This study is part of the Urban Health Centres Europe (UHCE) project which is aimed at promoting healthy ageing in older adults by means of integrated care pathways covering the adherence to medication, prevention of falls and frailty, and loneliness.[17, 18] Integrated care pathways were implemented in community settings at study sites in five European countries (Spain, Greece, Croatia, the Netherlands and the United Kingdom). At each study site, adults older than 70 years, who lived independently and were expected to be able to participate in the study for at least 6 months, were invited to participate. A total of 2325 participants were recruited between May 2015 and June 2017; 1215 were included in an integrated care pathway intervention; 1110 were enrolled in the control group. Participants in the

intervention group received care in accordance with the UHCE approach which comprised three stages: risk assessment, shared-decision making and referral to care pathways aimed at reducing fall risk, inappropriate medication use, loneliness and frailty by specific interventions.[18] Further details on these interventions are described elsewhere.[17, 18] Data were obtained from self-reported questionnaires at baseline and at 12 months of follow-up. Ethics committee procedures were followed at all study sites and approval was obtained.[17] Written informed consent was obtained from all participants.[17, 18]

The current study included participants in the UHCE project who had completed both baseline and follow-up questionnaires (n = 1844).[18] Participants in whom data on PA (n = 71) and frailty (n = 38) were missing were excluded. Thus, 1735 participants were included in the analyses of the current study.

Compared with the study population (n = 1735), the participants excluded from the study due to missing data on PA and frailty (n = 109) were younger (mean age = 77.1 years; SD = 6.1 years; *P* <. 001), had less often completed tertiary education (*P* = 0.016), more often lived alone (*P* < .001), and were less often at risk for alcohol use (*P* = 0.045). No other significant differences between these two groups were found.

Measurements

Physical activity

The frequency of moderate PA was measured by means of one question from the Frailty Instrument of the Survey of Health, Ageing and Retirement in Europe (SHARE-FI): "How often do you engage in activities that require a low or moderate level of energy such as gardening, cleaning the car, or taking a walk?".[19, 20] Answer categories included (a) more than once a week, (b) once a week, (c) one to three times a month and (d) hardly ever, or never. For our study, we classified these into two categories: 'Regular frequency' (more than once a week) and 'Low frequency' (once a week or less). We classified the change in the frequency of moderate PA between baseline and follow-up into four categories: (1) 'Continued regular frequency' (more than once a week), (2) 'Decreased frequency', (3) 'Continued low frequency' (once a week or less) and (4) 'Increased frequency'.

Frailty

Frailty was measured with the Tilburg Frailty Indicator (TFI), which is a reliable and validated instrument to identify frailty in community-dwelling older adults.[21] The TFI comprises 15 self-reported questions addressing three domains: physical frailty (8 items; score range 0-8), psychological frailty (4; 0-4) and social frailty (3; 0-3). An overall frailty score can be determined by adding up the 15 items (score range 0-15), with higher scores representing a higher level of frailty.[22]

Covariates

Some covariates were assessed at baseline, including age (in years), sex, country, educational level, living situation, smoking, alcohol risk and multi-morbidity. Educational level concerned the highest level of education completed by the participant and was categorized according to the 2011 International Standard Classification of Education (ISCED) into primary or less (ISCED 0-1), secondary or equivalent (ISCED 2-5), and tertiary or higher (ISCED 6-8).[23] Living situation was categorized as 'not living with others' or 'living with others' (a partner, child(ren) and/or others). Smoking was measured with one item that assessed whether a person currently smoked. Alcohol risk was measured with the Alcohol Use Disorder Identification Test (AUDIT-C),[24] which is a 3-item screener to grade high-risk alcohol use on a scale from 0 (lowest risk) to 12 (highest risk). A score of at least 4 for men and 3 for women was regarded as hazardous drinking or active alcohol use disorder.[24] Multi-morbidity was defined as having at least two of the following 14 chronic conditions[25]: heart attack, hypertension, diabetes, stroke, high blood cholesterol, asthma, arthritis, osteoporosis, chronic lung disease, cancer or malignant tumor, stomach or duodenal ulcer, Parkinson's disease, cataract and hip fracture or femoral fracture.[26]

Statistical analysis

The longitudinal association between frequency of moderate PA and frailty was estimated with multivariate linear regression models. Four separate regression models were built for overall, physical, psychological or social frailty at follow-up as dependent variable, and frequency of moderate PA at baseline as independent variable. The first set of models were adjusted for country and for frailty at baseline (*crude model*). The second set of models were additionally adjusted for age, sex, educational level, living situation, smoking, alcohol risk and multi-morbidity (*adjusted model*). Since the UHCE project was an intervention study and participants were divided over an intervention and a control group, intervention condition was also added to the adjusted mode as a covariate.

The association between the 12-month change in frequency of moderate PA and overall, physical, psychological or social frailty was assessed using the same crude and adjusted multivariate linear regression models as described above, taking change in frequency of moderate PA as the independent variable.

Furthermore, interactions between baseline frequency of moderate PA or 12-month change in frequency of moderate PA and age, sex, country, educational level, living situation and intervention on the frailty scores were assessed with UNIANOVA. Bonferroni correction was applied for multiple testing ($P = 0.05/48 = 0.001$). Apart from an interaction between country and change in frequency of moderate PA regarding psychological frailty, no statistically significant interaction was found. All *P*-values of the interaction analyses are presented in Supplementary Table S1.

Finally, sensitivity analyses were performed where all analyses were repeated using the participants in the control group only; we found similar results.

All analyses were performed with SPSS version 23.0 (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp). The level of significance was *P*-value<0.05.

RESULTS

Baseline characteristics of participants

Table 1 shows the general characteristics of the study population at baseline. The mean age of participants was 79.6 (SD = 5.5) years and 61.1% were female. Compared with participants who undertook moderate PA with a regular frequency, participants with a low frequency of moderate PA were older ($P < .001$), were more often female ($P < .001$), had less often completed tertiary level education ($P < .001$), were less often at risk for alcohol use ($P < .001$) and more often suffered from multi-morbidity ($P = 0.004$).

Figure 1 shows the frequency of moderate PA of participants at baseline and follow-up as well as change in frequency of moderate PA. At baseline, 1272 participants reported undertaking moderate PA with a regular frequency. Of these, 1020 (58.8% of the study population) continued this regular frequency after 12 months of follow-up and in 252 (14.5%) had decreased their exercise to low frequency. Of the 463 participants who undertook moderate PA with a low frequency at baseline, 302 (17.4%) continued this low frequency after 12 months of follow-up, and 161 (9.3%) had increased their exercise to a regular frequency.

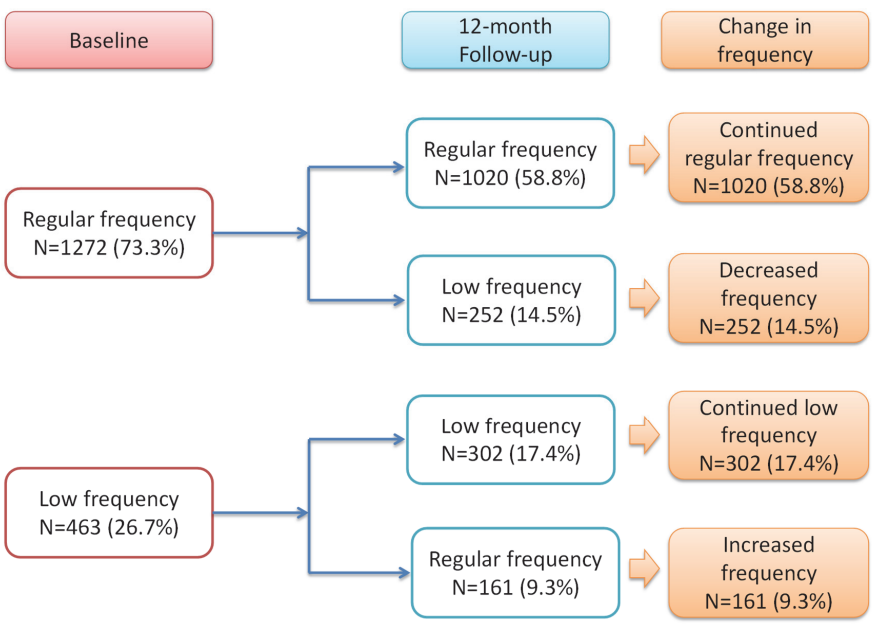

Figure 1 Frequency of moderate physical activity of participants

Table 1 Baseline characteristics of participants in the analyses (n=1735)

Items	Total (n=1735)	Baseline frequency of moderate PA		12-month change in moderate PA			
		Regular frequency (n=1272)	Low frequency (n=463)	Continued regular frequency (n=1020)	Decreased frequency (n=252)	Continued low frequency (n=302)	Increased frequency (n=161)
Age	79.6±5.5	79.1±5.3[a]	81.2±5.8[a]	78.8±5.2[b]	80.3±5.6[b]	81.9±5.9[b]	79.9±5.4[b]
Sex							
Male	675(38.9)	532(41.8)[b]	143(30.9)[b]	430(42.2)[b]	102(40.5)[b]	84(27.8)[b]	59(36.6)[b]
Female	1060(61.1)	740(58.2)[b]	320(69.1)[b]	590(57.8)[b]	150(59.5)[b]	218(72.2)[b]	102(63.4)[b]
Country							
Spain	394(22.7)	327(25.7)[c]	67(14.5)[c]	288(28.2)[c]	39(15.5)[c]	25(8.3)[c]	42(26.1)[c]
Greece	209(12.0)	149(11.7)[c]	60(13.0)[c]	101(9.9)[c]	48(19.0)[c]	44(14.6)[c]	16(9.9)[c]
Croatia	418(24.1)	255(20.0)[c]	163(35.2)[c]	185(18.1)[c]	70(27.8)[c]	128(42.4)[c]	35(21.7)[c]
NL	265(15.3)	203(16.0)[c]	62(13.4)[c]	161(15.8)[c]	42(16.7)[c]	30(9.9)[c]	32(19.9)[c]
UK	449(25.9)	338(26.6)[c]	111(24.0)[c]	285(27.9)[c]	53(21.0)[c]	75(24.8)[c]	36(22.4)[c]
Educational level							
Tertiary	173(10.0)	147(11.6)[c]	26(5.6)[c]	110(10.8)[c]	37(14.7)[c]	15(5.0)[c]	11(6.9)[c]
Secondary	1125(65.1)	790(62.4)[c]	335(72.7)[c]	638(62.9)[c]	152(60.6)[c]	228(75.5)[c]	107(67.3)[c]
Primary or less	429(24.8)	329(26.0)[c]	100(21.7)[c]	267(26.3)[c]	62(24.7)[c]	59(19.5)[c]	41(25.8)[c]
Living situation							
Living with others	1054(60.9)	790(62.2)	264(57.4)	631(62.0)	159(63.1)	170(56.3)	94(59.5)
Living alone	676(39.1)	480(37.8)	196(42.6)	387(38.0)	93(36.9)	132(43.7)	64(40.5)
Smoking							
No	1601(92.4)	1166(91.7)	435(94.4)	941(92.3)	225(89.3)	284(94.7)	151(93.8)
Yes	131(7.6)	105(8.3)	26(5.6)	78(7.7)	27(10.7)	16(5.3)	10(6.2)
Alcohol risk							
No	1198(72.6)	823(68.5)[c]	375(83.7)[c]	660(68.1)[c]	163(70.0)[c]	255(87.3)[c]	120(76.9)[c]
Yes	452(27.4)	379(31.5)[c]	73(16.3)[c]	309(31.9)[c]	70(30.0)[c]	37(12.7)[c]	36(23.1)[c]
Multi-morbidity							
No	162(9.3)	134(10.5)[d]	28(6.0)[d]	113(11.1)[d]	21(8.3)[d]	12(4.0)[d]	16(9.9)[d]
Yes	1573(90.7)	1138(89.5)[d]	435(94.0)[d]	907(88.9)[d]	231(91.7)[d]	290(96.0)[d]	145(90.1)[d]

Note: Data presented as mean±SD or number (percentage). Missing items: Age=1; Education level=8; Living situation=5; Smoking=3; Alcohol risk=85.

Abbreviations: PA, physical activity; NL, the Netherlands; UK, the United Kingdom.

[a] $p<.001$; *P* values are based on independent T test

[b] $p<.001$; *P* values are based on one-way analysis of variance (ANOVA)

[c] $p<.001$; *P* values are based on χ^2 tests

[d] $p<.01$; *P* values are based on χ^2 tests

Table 2 Overall, physical, psychological and social frailty at baseline and follow-up

Groups of PA	Baseline	Follow-up	*P*-value[a]
	Overall frailty score (score range 0-15)		
Baseline frequency of PA			
Regular frequency (n=1272)	4.45±2.91[b]	4.56±3.16[b]	0.122
Low frequency (n=463)	6.96±3.07[b]	6.80±3.27[b]	0.165
12-month change in PA			
Continued regular frequency (n=1020)	4.18±2.78[c]	4.10±2.95[c]	0.337
Decreased frequency (n=252)	5.57±3.18[c]	6.39±3.34[c]	***P*<.001**
Continued low frequency (n=302)	7.42±2.93[c]	7.67±2.95[c]	0.069
Increased frequency (n=161)	6.10±3.16[c]	5.18±3.22[c]	***P*<.001**
	Physical frailty score (score range 0-8)		
Baseline frequency of PA			
Regular frequency (n=1272)	2.51±1.96[b]	2.55±2.16[b]	0.409
Low frequency (n=463)	4.20±2.05[b]	3.99±2.13[b]	**0.009**
12-month change in PA			
Continued regular frequency (n=1020)	2.33±1.88[c]	2.27±2.04[c]	0.313
Decreased frequency (n=252)	3.26±2.12[c]	3.68±2.67[c]	***P*<.001**
Continued low frequency (n=302)	4.55±1.91[c]	4.54±1.90[c]	0.930
Increased frequency (n=161)	3.56±2.16[c]	2.94±2.17[c]	***P*<.001**
	Psychological frailty score (score range 0-4)		
Baseline frequency of PA			
Regular frequency (n=1272)	1.00±1.00[b]	1.06±1.08[b]	0.052
Low frequency (n=463)	1.52±1.10[b]	1.61±1.20[b]	0.092
12-month change in PA			
Continued regular frequency (n=1020)	0.94±0.97[c]	0.92±1.01[c]	0.550
Decreased frequency (n=252)	1.25±1.06[c]	1.60±1.20[c]	***P*<.001**
Continued low frequency (n=302)	1.64±1.13[c]	1.85±1.21[c]	***P*<.001**
Increased frequency (n=161)	1.30±1.02[c]	1.15±1.05[c]	0.103
	Social frailty score (score range 0-3)		
Baseline frequency of PA			
Regular frequency (n=1272)	0.94±0.88[b]	0.95±0.88[b]	0.601
Low frequency (n=463)	1.24±0.90[b]	1.21±0.89[b]	0.485
12-month change in PA			
Continued regular frequency (n=1020)	0.91±0.86[c]	0.90±0.87[c]	0.898
Decreased frequency (n=252)	1.05±0.96[c]	1.12±0.91[c]	0.197
Continued low frequency (n=302)	1.23±0.91[c]	1.28±0.88[c]	0.266
Increased frequency (n=161)	1.25±0.89[c]	1.08±0.90[c]	**0.011**

Note: Data presented as mean±SD; a higher score represents a higher level of frailty.

Abbreviations: PA, physical activity.

[a] Significant *P* values in bold; paired *t* test.

[b] *p*<.001; *P* values are based on independent *t* test.

[c] *p*<.001; *P* values are based on one-way analysis of variance.

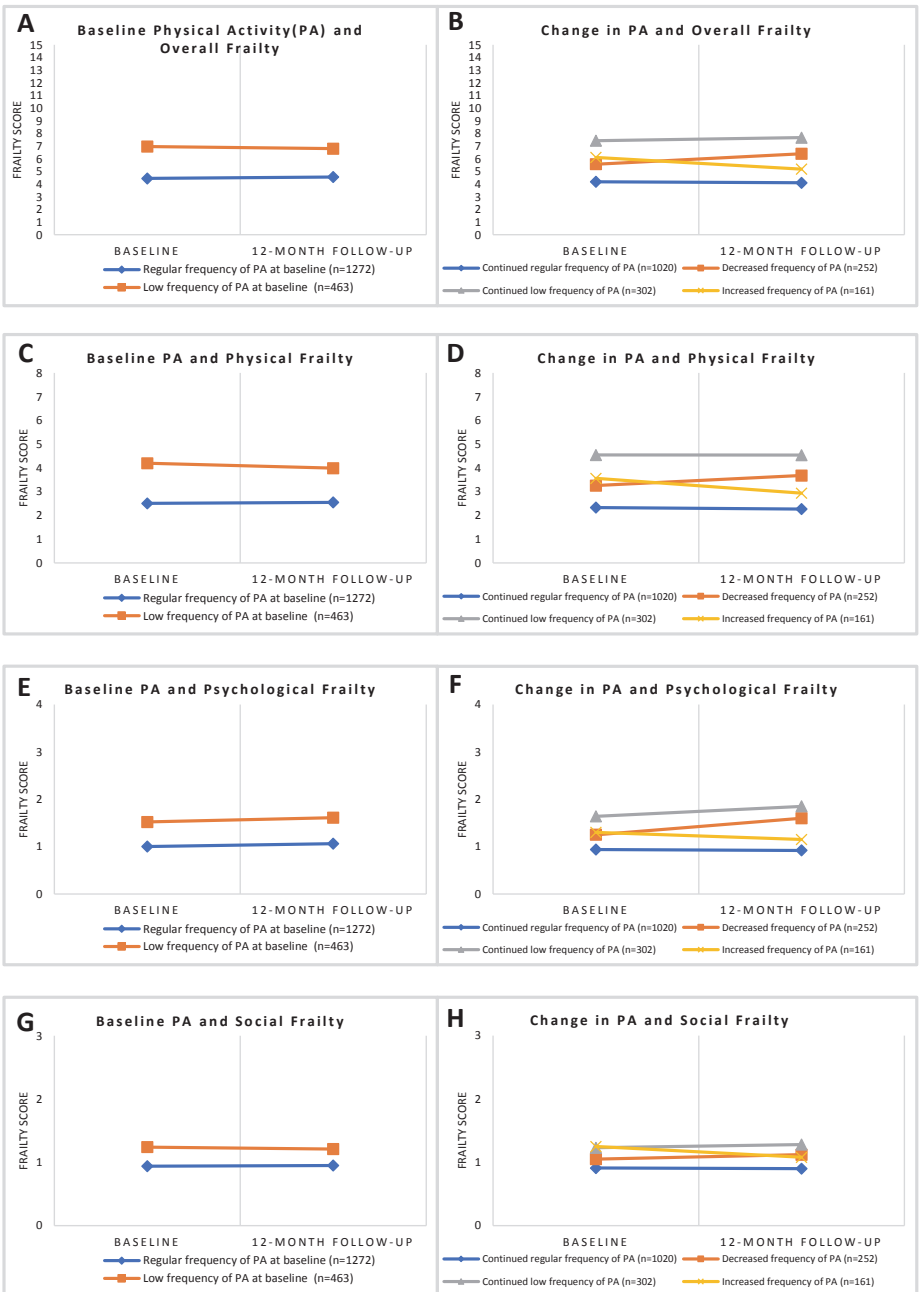

Figure 2 Frailty score at baseline and follow-up of participants from the groups of frequency of moderate physical activity (PA)

(A) Baseline PA and overall frailty, (B) Change in PA and overall frailty, (C) Baseline PA and physical frailty, (D) Change in PA and physical frailty, (E) Baseline PA and psychological frailty, (F) Change in PA and psychological frailty, (G) Baseline PA and social frailty, (H) Change in PA and social frailty.

Frailty at baseline and follow-up

Table 2 and Figure 2 show the overall, physical, psychological and social frailty scores at baseline and follow-up by 1) frequency of moderate PA at baseline, and 2) 12-month change in frequency of moderate PA. Compared with participants who undertook moderate PA with a regular frequency at baseline, participants who undertook moderate PA with a low frequency were significantly more overall (mean = 6.80; SD = 3.27; Figure 2, Part A), physically (mean = 3.99; SD = 2.13; Figure 2, Part C), psychologically (mean = 1.61; SD = 1.20; Figure 2, Part E) and socially (mean = 1.21; SD = 0.89; Figure 2, Part G) frail at follow-up.

Regarding change in frequency of moderate PA, those participants who undertook moderate PA with a continued regular frequency were least frail, and participants with a continued low frequency were most frail at follow-up (Figure 2, Part B, D, F and H). Participants who undertook moderate PA with a decreased frequency were more frail at follow-up than at baseline (Figure 2, Part B, D, and F). However, the difference in social frailty was not significant. Conversely, participants who undertook moderate PA with an increased frequency were less frail at follow-up than at baseline (Figure 2, Part B, D, and H), although the difference in psychological frailty was not significant.

Association between frequency of moderate PA and frailty

Supplementary Table S2 shows the multivariate linear regression models exploring the association between frequency of moderate PA at baseline and overall, physical, psychological or social frailty at follow-up. Compared with participants who undertook moderate PA with a regular frequency at baseline, participants with low exercise frequency were significantly more frail (B = 0.28; 95%CI = 0.01,0.55; $P < 0.05$) at follow-up after controlling for overall frailty at baseline and the covariates.

Association between 12-month change in frequency of moderate PA and frailty

Table 3 shows the multivariate linear regression models exploring the association between 12-month change in frequency of moderate PA and overall, physical, psychological or social frailty at follow-up. Change in frequency of moderate PA was significantly associated with overall, physical, psychological and social frailty at follow-up.

Compared with participants who undertook moderate PA with a continued regular frequency, participants with a decreased frequency (B = 1.31; 95%CI = 0.99,1.63; $P < .001$) and participants with a continued low frequency (B = 1.16; 95%CI = 0.84,1.49; $P < .001$) were significantly more overall frail at follow-up after the covariates and overall frailty at baseline were controlled. Regarding physical frailty, participants with a decreased frequency (B = 0.80; 95%CI = 0.58,1.03; $P < .001$) and participants with a continued low frequency (B = 0.73; 95%CI = 0.51,0.96; $P < .001$) were significantly more physically frail at follow-up. Regarding psychological frailty, participants with a decreased frequency (B = 0.43; 95%CI = 0.30,0.56; $P < .001$) and participants with a continued low frequency (B = 0.42; 95%CI = 0.29,0.55; $P<.001$) were significantly more psychologically frail at follow-up. Regarding social frailty, participants

with decreased exercise frequency (B = 0.14; 95%CI = 0.04,0.23; *P*<0.01) and participants with a continued low frequency (B = 0.13; 95%CI = 0.04,0.23; *P*<0.01) were significantly more socially frail at follow-up. There was no significant difference in overall, physical, psychological and social frailty at follow-up between participants who undertook moderate PA with an increased frequency and participants with a continued regular frequency. More details can be found in Supplementary Table S3.

Table 3 Multivariate linear regression models (12-month change in physical activity and follow-up scores of frailty)

12-month follow-up frailty score	12-month change in moderate physical activity				
	Continued regular frequency	Decreased frequency	Continued low frequency	Increased frequency	Adjusted R^2, %
Overall frailty					
Crude Model[d]	*Reference*	**1.34[c](1.02,1.66)**	**1.31[c](1.00,1.63)**	-0.25(-0.64,0.13)	56.6
Adjusted Model[e]	*Reference*	**1.31[c](0.99,1.63)**	**1.16[c](0.84,1.49)**	-0.25(-0.63,0.14)	57.8
Physical frailty					
Crude Model[f]	*Reference*	**0.83[c](0.60,1.06)**	**0.86[c](0.63,1.09)**	-0.15(-0.42,0.12)	51.6
Adjusted Model[g]	*Reference*	**0.80[c](0.58,1.03)**	**0.73[c](0.51,0.96)**	-0.15(-0.42,0.11)	53.0
Psychological frailty					
Crude Model[h]	*Reference*	**0.45[c](0.32,0.58)**	**0.47[c](0.35,0.60)**	0.02(-0.13,0.18)	39.2
Adjusted Model[i]	*Reference*	**0.43[c](0.30,0.56)**	**0.42[c](0.29,0.55)**	0.01(-0.15,0.16)	39.7
Social frailty					
Crude Model[j]	*Reference*	**0.13[a](0.03,0.23)**	**0.14[b](0.05,0.24)**	-0.03(-0.15,0.09)	41.8
Adjusted Model[k]	*Reference*	**0.14[b](0.04,0.23)**	**0.13[b](0.04,0.23)**	0.02(-0.09,0.13)	48.5

Note: Data presented as B(95% confidence interval), unless otherwise indicated. More details can be found in Supplementary Table S3.

[a] *p*<.05, [b] *p*<.01, [c] *p*<.001, significant effect estimates in bold

[d] Adjusted for baseline overall frailty and country

[e] Adjusted for baseline overall frailty, country, age, sex, education level, living situation, smoking, alcohol risk, multi-morbidity and intervention condition

[f] Adjusted for baseline physical frailty and country

[g] Adjusted for baseline physical frailty, country, age, sex, education level, living situation, smoking, alcohol risk, multi-morbidity and intervention condition

[h] Adjusted for baseline psychological frailty and country

[i] Adjusted for baseline psychological frailty, country, age, sex, education level, living situation, smoking, alcohol risk, multi-morbidity and intervention condition

[j] Adjusted for baseline social frailty and country

[k] Adjusted for baseline social frailty, country, age, sex, education level, living situation, smoking, alcohol risk, multi-morbidity and intervention condition

DISCUSSION

Our study aimed to examine the longitudinal association between the frequency of moderate PA and frailty among community-dwelling older adults older than 70 years. We found that participants who undertook moderate PA with a regular frequency at baseline were less overall frail at follow-up than participants with a low frequency. Second, we assessed the association between a 12-month change in frequency of moderate PA and frailty. Older adults who undertook moderate PA with an increased frequency were less overall frail at follow-up than they were at baseline. Older adults who undertook moderate PA with a continued regular frequency were least overall frail at baseline and at 12-month follow-up. Interestingly, after controlling all the covariates and baseline overall frailty, the follow-up overall frailty levels of participants who undertook moderate PA with an increased frequency were similar to those with a continued regular frequency. These findings indicate that maintaining a regular frequency of PA as well as increasing frequency of PA are associated with maintaining or improving overall frailty (multidimensional).

Previous observational studies[3, 10, 15] also found that PA is associated with a delay in progression of frailty among older adults, but these studies focused on physical frailty. More studies on multidimensional frailty are still needed. Additionally, some randomized controlled trials (RCTs) on the effect of PA intervention on physical frailty showed conflicting results. An RCT among 424 older adults found that regular PA could reduce the presence and severity of physical frailty, especially in individuals at higher risk of disability.[9] In contrast, a secondary analysis of an RCT among 1635 older adults reported that a structured, moderate-intensity PA program was not associated with a reduction in the overall risk of physical frailty.[12] These differing results may be due to the different characteristics of PA intervention methods (e.g. the intensity, frequency and duration of PA) as well as differing frailty criteria among studies.[7, 12] RCTs that study the effect of various kinds of PA intervention (e.g. moderate or vigorous activity or a combination of both with different frequency and duration) on frailty are needed to determine the optimal level of PA among older adults.

In addition to overall and physical frailty, our findings report on the longitudinal association between PA and psychological and social frailty. After controlling all the covariates and baseline frailty, we found that older adults who undertook moderate PA with a continued regular frequency were least psychologically and socially frail at baseline and follow-up, and that the follow-up psychological and social frailty levels of participants who undertook moderate PA with an increased frequency were similar to those with a continued regular frequency. Regarding psychological frailty, a controlled study of older adults aged 61 to 89 years in Canada found that PA training could improve cognitive functioning and psychological well-being.[27] A systematic review of 11 RCTs to assess the effect of PA on depression found that PA may reduce depression or depressive symptoms in adults older than 60 years.[28] A qualitative study among older adults aged 80 to 91 years in Sweden reported that PA could help older adults to have the energy to be active and to improve their mood, because PA was

able help them realize that their body was still working well enough to perform the activity.[29] Regarding social frailty, an RCT in Spain found that a multicomponent exercise program was not only able to improve the physical aspects of frailty, but also to increase interaction with other people which could reduce the level of social frailty.[30, 31] However, studies to investigate the association between PA and psychological and social frailty among older adults are still scarce and more studies are needed.[27, 32]

Finally, regarding psychological frailty, we found an interaction between 12-month change in moderate PA and country; in the Netherlands the results were different from the results from the other four countries (see Supplementary Table S4). More studies are needed to clarify this finding.

Strengths and limitations

One strength of our study is that we added longitudinal evidence on the association between PA and frailty among citizens aged 70 years or older from a diverse community-based sample from five European countries. In addition, we used a validated instrument in order to consider frailty broadly from the physical, psychological and social perspectives, and to add to the current literature on the association between change in PA and the three domains of frailty. Social frailty in particular is a rarely explored domain and there is a dearth of studies on this subject.[33, 34]

However, our study also has some limitations. First, PA was measured by one self-reported question which is fairly crude and open to interpretation. This question does not differentiate between type of activity and does not take the duration of activity into account. Studies using a more comprehensive measurement of PA are needed to confirm our findings. However, some previous studies[35-37] indicate that using a single question to measure PA is acceptable under certain conditions, e.g. when the sample size is large, when more complex methods would add to respondent burden, and when collecting data from a broad range of settings. Grill et al. (2012) also suggest that the reliability and validity of a single question to briefly classify PA levels is acceptable.[38] Therefore, taking into account the large sample size, the response burden and the aim of the study, we believe that using a single question to measure the frequency of PA is acceptable. Second, we transferred the ordinal variable of PA into a dichotomous one which might cause information loss. However, we conducted additional analyses on the association between PA and frailty with the ordinal variable of PA (Supplementary Figure S1), and the results were similar to our primary findings. Third, we found statistically significant differences in frailty scores between baseline and follow-up. This finding was based on statistical methods rather than on clinical examinations. Hence, we cannot draw conclusions on the clinical meaning of the TFI scores. Future studies should explore whether this statistical difference corresponds to a clinically meaningful change in frailty level. Fourth, participants in both the intervention and control groups were included in the analyses. The intervention may have led to improvement in health which could result in the over-estimation of the effect of PA on frailty. However, we controlled for the intervention

condition by adding it to the regression models as a covariate. We also repeated the analyses for the control group only and found similar results. Additionally, we considered the results of those persons who had received specific UHCE interventions may have had an effect on the changes in the frequency of PA. Therefore, we conducted a sensitivity analysis to control for specific UHCE interventions that may promote PA. For this purpose, the intervention condition in the multivariable regression model was categorized into three categories instead of two: (1) control group, (2) intervention promoting PA group (participants who enrolled in the falls and/or frailty pathway, and (3) intervention not promoting PA group (participants who did not enroll in the falls and/or frailty pathway). The results of this sensitivity analysis were similar to our primary findings. Fifth, our observational study cannot confirm causality between PA and frailty. A decrease in frequency of PA might be the cause of the progression of frailty, or simply the epiphenomenon of a declining health status. In addition, a decrease in PA might also have been caused by external factors leading to frailty, such as an accident, stroke or fall during the year. Adjusting for multi-morbidity at baseline, only partly reflects these variations of PA during 12-month follow-up. Sixth, over adjustment bias may exist because we adjusted for many covariates and some of these (e.g. multi-morbidity) may act partially as a confounder and partially as a mediator. Last, there may be overlap between PA and two items of the TFI (walking and balance) which could cause over-estimation of the association. However, when we explored the association between PA and overall frailty, after deleting these two items the results were similar. Hence, we do not expect that this limitation has changed our findings.

CONCLUSIONS

In conclusion, we found that both maintaining a regular frequency of PA and increasing to a regular frequency of PA are associated with maintaining or improving the level of frailty among European community-dwelling older adults older than 70 years, not only in the physical domain, but also in the psychological and social domains of frailty. Our findings support the development of new public health strategies to encourage adults older than 70 years to maintain a regular frequency of PA to prevent and delay not only physical but also psychological and social frailty. More RCTs studying the effect of the frequency and intensity levels of PA are needed to determine the optimum level of PA required to prevent the progression of physical, psychological and social frailty among older adults.

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Supplementary Table S1 *P*-values for interactions between baseline frequency of moderate PA or 12-month change in frequency of moderate PA and age, sex, county, educational level, living situation and intervention on the frailty scores

Items	Overall frailty	Physical frailty	Psychological frailty	Social frailty
	***P*-value**	***P*-value**	***P*-value**	***P*-value**
Interactions in models on associations between baseline frequency of moderate PA and frailty				
Baseline frequency of moderate PA*Age	0.452	0.193	0.838	0.350
Baseline frequency of moderate PA*Sex	0.692	0.754	0.878	0.877
Baseline frequency of moderate PA*Country	0.409	0.142	0.346	0.705
Baseline frequency of moderate PA*Educational level	0.923	0.885	0.658	0.056
Baseline frequency of moderate PA* Live situation	0.926	0.966	0.497	0.924
Baseline frequency of moderate PA*Intervention	0.142	0.269	0.303	0.479
Interactions in models on associations between 12-month change in moderate PA and frailty				
Change in moderate PA*Age	0.443	0.216	0.838	0.546
Change in moderate PA*Sex	0.766	0.928	0.682	0.943
Change in moderate PA*Country	0.136	0.189	**<0.001**	0.856
Change in moderate PA*Educational level	0.719	0.542	0.117	0.148
Change in moderate PA*Live situation	0.682	0.272	0.089	0.022
Change in moderate PA*Intervention	0.399	0.743	0.714	0.329

Note: Significant *P*-values in bold

After applying Bonferroni correction for multiple testing (P=0.05/48=0.001), except interaction between country and change in physical activity on follow-up psychological frailty score, no statistically significant interaction was found.

Abbreviations: PA, physical activity

Supplementary Table S2 Multivariate linear regression models (frequency of moderate physical activity at baseline and follow-up scores of frailty)

Items	12-month follow-up overall frailty		12-month follow-up physical frailty		12-month follow-up psychological frailty		12-month follow-up social frailty	
	Crude Model B(95%CI)	Adjusted Model B(95%CI)	Crude Model B(95%CI)	Adjusted Model B(95%CI)	Crude Model B(95%CI)	Adjusted Model B(95%CI)	Crude Model B(95%CI)	Adjusted Model B(95%CI)
Baseline frequency of moderate physical activity								
Regular frequency	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*
Low frequency	**0.39[b](0.13,0.66)**	**0.28[a](0.01,0.55)**	**0.27[b](0.08,0.45)**	0.18(-0.01,0.37)	**0.21[c](0.10,0.31)**	**0.16[b](0.05,0.27)**	0.05(-0.02,0.13)	0.06(-0.02,0.13)
Baseline overall frailty	**0.69[c](0.65,0.73)**	**0.65[c](0.61,0.69)**						
Baseline physical frailty			**0.66[c](0.62,0.70)**	**0.62[c](0.58,0.67)**				
Baseline psychological frailty					**0.56[c](0.51,0.60)**	**0.54[c](0.50,0.59)**		
Baseline social frailty							**0.62[c](0.59,0.66)**	**0.39[c](0.34,0.44)**
Age		**0.04[c](0.02,0.07)**		**0.03[b](0.01,0.04)**		**0.01[a](0.00,0.02)**		0.01(-0.00,0.01)
Sex								
Male		*Reference*		*Reference*		*Reference*		*Reference*
Female		0.24(-0.01,0.48)		0.11(-0.06,0.29)		**0.12[a](0.02,0.22)**		0.04(-0.03,0.11)
Country								
Spain	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*
Greece	-0.05(-0.46,0.36)	-0.20(-0.21,0.62)	-0.21(-0.50,0.07)	-0.08(-0.37,0.21)	**0.18[a](0.02,0.35)**	**0.25[b](0.08,0.42)**	0.08(-0.04,0.20)	**0.21[b](0.09,0.33)**
Croatia	**0.83[c](0.50,1.17)**	**0.96[c](0.57,1.36)**	**0.44[c](0.20,0.67)**	**0.54[c](0.26,0.81)**	**0.32[c](0.19,0.45)**	**0.35[c](0.19,0.51)**	**0.17[b](0.07,0.27)**	**0.22[b](0.10,0.33)**
The Netherlands	-0.19(-0.55,0.18)	-0.08(-0.49,0.32)	-0.11(-0.37,0.14)	0.01(-0.28,0.29)	**-0.16[a](-0.30,-0.01)**	-0.11(-0.27,0.05)	0.05(-0.06,0.16)	-0.01(-0.11,0.12)
The United Kingdom	**-0.45[b](-0.76,-0.14)**	**-0.45[a](-0.84,-0.07)**	**-0.45[c](-0.67,-0.23)**	**-0.43[b](-0.70,-0.16)**	**-0.15[a](-0.28,-0.03)**	-0.10(-0.26,0.05)	**0.12[a](0.02,0.21)**	0.04(-0.07,0.15)
Educational level								
Tertiary or higher		*Reference*		*Reference*		*Reference*		*Reference*
Secondary or equivalent		0.12(-0.26,0.51)		0.13(-0.14,0.40)		0.04(-0.12,0.19)		-0.00(-0.11,0.11)
Primary or less versus		**0.55[a](0.11,0.98)**		**0.40[a](0.10,0.71)**		0.17(-0.01,0.34)		0.07(-0.06,0.19)
Living situation								
Living with others		*Reference*		*Reference*		*Reference*		*Reference*

Supplementary Table S2 Multivariate linear regression models (frequency of moderate physical activity at baseline and follow-up scores of frailty) (Continued)

Items	12-month follow-up overall frailty		12-month follow-up physical frailty		12-month follow-up psychological frailty		12-month follow-up social frailty	
	Crude Model B(95%CI)	Adjusted Model B(95%CI)	Crude Model B(95%CI)	Adjusted Model B(95%CI)	Crude Model B(95%CI)	Adjusted Model B(95%CI)	Crude Model B(95%CI)	Adjusted Model B(95%CI)
Living alone		0.06(-0.19,0.31)		-0.12(-0.29,0.06)		**-0.13[b](-0.23,-0.03)**		**0.61[c](0.52,0.70)**
Smoking								
No		*Reference*		*Reference*		*Reference*		*Reference*
Yes		0.02(-0.39,0.43)		-0.15(-0.44,0.14)		0.11(-0.06,0.27)		0.07(-0.05,0.18)
Alcohol risk								
No		*Reference*		*Reference*		*Reference*		*Reference*
Yes		-0.23(-0.48,0.02)		-0.08(-0.26,0.10)		**-0.12[a](-0.22,-0.01)**		-0.06(-0.13,0.02)
Multi-morbidity								
No		*Reference*		*Reference*		*Reference*		*Reference*
Yes		**0.59[b](0.20,0.97)**		**0.50[c](0.22,0.77)**		0.10(-0.06,0.25)		0.07(-0.04,0.18)
Intervention condition								
Control group		*Reference*		*Reference*		*Reference*		*Reference*
Intervention group		**-0.50[c](-0.72,-0.28)**		**-0.42[c](-0.58,-0.27)**		-0.05(-0.14,0.04)		-0.02(-0.08,0.05)
Adjusted R^2, %	53.7	55.2	49.0	50.8	36.7	37.5	41.4	48.2

[a] $p<.05$, [b] $p<.01$, [c] $p<.001$, significant effect estimates in bold

Supplementary Table S3 Multivariate linear regression models (12-month change in physical activity and follow-up scores of frailty)

Items	12-month follow-up overall frailty		12-month follow-up physical frailty		12-month follow-up psychological frailty		12-month follow-up social frailty	
	Crude Model B(95%CI)	Adjusted Model B(95%CI)	Crude Model B(95%CI)	Adjusted Model B(95%CI)	Crude Model B(95%CI)	Adjusted Model B(95%CI)	Crude Model B(95%CI)	Adjusted Model B(95%CI)
12-month change in moderate physical activity								
Continued regular frequency	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*
Decreased frequency	**1.34[c](1.02,1.66)**	**1.31[c](0.99,1.63)**	**0.83[c](0.60,1.06)**	**0.80[c](0.58,1.03)**	**0.45[c](0.32,0.58)**	**0.43[c](0.30,0.56)**	**0.13[a](0.03,0.23)**	**0.14[b](0.04,0.23)**
Continued low frequency	**1.31[c](1.00,1.63)**	**1.16[c](0.84,1.49)**	**0.86[c](0.63,1.09)**	**0.73[c](0.51,0.96)**	**0.47[c](0.35,0.60)**	**0.42[c](0.29,0.55)**	**0.14[b](0.05,0.24)**	**0.13[b](0.04,0.23)**
Increased frequency	-0.25(-0.64,0.13)	-0.25(-0.63,0.14)	-0.15(-0.42,0.12)	-0.15(-0.42,0.11)	0.02(-0.13,0.18)	0.01(-0.15,0.16)	-0.03(-0.15,0.09)	0.02(-0.09,0.13)
Baseline overall frailty	**0.66[c](0.62,0.70)**	**0.62[c](0.58,0.66)**						
Baseline physical frailty			**0.62[c](0.58,0.66)**	**0.60[c](0.55,0.64)**				
Baseline psychological frailty					**0.54[c](0.50,0.59)**	**0.53[c](0.48,0.57)**		
Baseline social frailty							**0.62[c](0.59,0.66)**	**0.39[c](0.34,0.44)**
Age		**0.03[a](0.00,0.05)**		**0.02[a](0.00,0.03)**		0.01(-0.00,0.02)		0.00(-0.00,0.01)
Sex								
Male		*Reference*		*Reference*		*Reference*		*Reference*
Female		0.20(-0.05,0.44)		0.09(-0.08,0.26)		**0.10[a](0.00,0.20)**		0.04(-0.03,0.11)
Country								
Spain	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*
Greece	-0.34(-0.74,0.06)	-0.10(-0.51,0.30)	**-0.41[b](-0.70,-0.13)**	-0.29(-0.57,0.00)	0.09(-0.07,0.26)	0.15(-0.02,0.32)	0.05(-0.08,0.17)	**0.17[b](0.05,0.29)**
Croatia	**0.56[b](0.23,0.88)**	**0.74[c](0.36,1.13)**	**0.26[a](0.03,0.49)**	**0.40[b](0.13,0.67)**	**0.22[b](0.09,0.36)**	**0.27[b](0.12,0.43)**	**0.14[b](0.04,0.24)**	**0.19[b](0.08,0.30)**
The Netherlands	-0.33(-0.68,0.02)	-0.19(-0.58,0.21)	-0.21(-0.46,0.04)	-0.06(-0.34,0.22)	**-0.20[b](-0.35,-0.06)**	-0.14(-0.30,0.02)	0.04(-0.07,0.15)	-0.00(-0.12,0.11)
The United Kingdom	**-0.61[c](-0.91,-0.30)**	**-0.55[b](-0.92,-0.17)**	**-0.55[c](-0.77,-0.34)**	**-0.49[c](-0.75,-0.22)**	**-0.20[b](-0.32,-0.08)**	-0.13(-0.28,0.02)	**0.10[a](0.01,0.19)**	0.03(-0.08,0.14)
Educational level								
Tertiary or higher		*Reference*		*Reference*		*Reference*		*Reference*
Secondary or equivalent		0.22(-0.15,0.60)		0.19(-0.08,0.45)		0.07(-0.09,0.22)		0.01(-0.10,0.12)
Primary or less versus		**0.63[b](0.20,1.05)**		**0.46[b](0.16,0.75)**		**0.19[a](0.01,0.36)**		0.08(-0.05,0.20)

Supplementary Table S3 Multivariate linear regression models (12-month change in physical activity and follow-up scores of frailty) (Continued)

Items	12-month follow-up overall frailty		12-month follow-up physical frailty		12-month follow-up psychological frailty		12-month follow-up social frailty	
	Crude Model B(95%CI)	Adjusted Model B(95%CI)	Crude Model B(95%CI)	Adjusted Model B(95%CI)	Crude Model B(95%CI)	Adjusted Model B(95%CI)	Crude Model B(95%CI)	Adjusted Model B(95%CI)
Living situation								
Living with others		*Reference*		*Reference*		*Reference*		*Reference*
Living alone		0.15(-0.10,0.39)		-0.08(-0.25,0.09)		**-0.11[a](-0.21,-0.02)**		**0.62[c](0.53,0.70)**
Smoking								
No		*Reference*		*Reference*		*Reference*		*Reference*
Yes		-0.02(-0.41,0.38)		-0.17(-0.45,0.12)		0.09(-0.07,0.26)		0.06(-0.06,0.18)
Alcohol risk								
No		*Reference*		*Reference*		*Reference*		*Reference*
Yes		-0.21(-0.45,0.04)		-0.07(-0.24,0.10)		**-0.11[a](-0.21,-0.01)**		-0.05(-0.12,0.02)
Multi-morbidity								
No		*Reference*		*Reference*		*Reference*		*Reference*
Yes		**0.50[a](0.12,0.87)**		**0.45[b](0.18,0.71)**		0.06(-0.10,0.21)		0.05(-0.06,0.16)
Intervention condition								
Control group		*Reference*		*Reference*		*Reference*		*Reference*
Intervention group		**-0.46[c](-0.68,-0.25)**		**-0.39[c](-0.55,-0.24)**		-0.04(-0.13,0.05)		-0.01(-0.08,0.05)
Adjusted R^2, %	56.6	57.8	51.6	53.0	39.2	39.7	41.8	48.5

[a] $p<.05$, [b] $p<.01$, [c] $p<.001$, significant effect estimates in bold

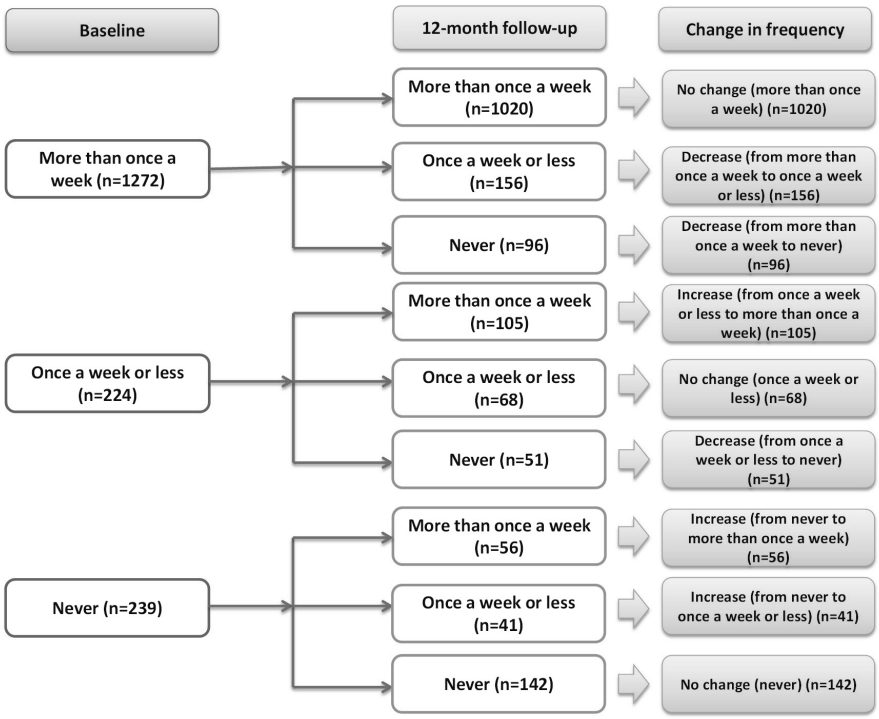
Supplementary Table S4 Multiple linear regression models (12-month change in moderate physical activity and psychological frailty) stratified by country

Items	Spain 12-month follow-up Psychological frailty		Greece 12-month follow-up Psychological frailty		Croatia 12-month follow-up Psychological frailty		The Netherlands 12-month follow-up Psychological frailty		The United Kingdom 12-month follow-up Psychological frailty	
	Crude Model B(95%CI)	Adjusted Model B(95%CI)	Crude Model B(95%CI)	Adjusted Model B(95%CI)	Crude Model B(95%CI)	Adjusted Model B(95%CI)	Crude Model B(95%CI)	Adjusted Model B(95%CI)	Crude Model B(95%CI)	Adjusted Model B(95%CI)
12-month change in moderate physical activity										
Continued regular frequency	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*
Decreased frequency	**0.55[c](0.25,0.85)**	**0.57[b](0.26,0.87)**	**0.67[c](0.30,1.04)**	**0.69[b](0.30,1.08)**	**0.50[b](0.21,0.79)**	**0.48[b](0.19,0.77)**	0.09(-0.19,0.37)	0.06(-0.23,0.35)	**0.50[c](0.25,0.74)**	**0.46[c](0.22,0.71)**
Continued low frequency	**0.80[c](0.43,1.16)**	**0.79[c](0.42,1.16)**	**0.93[c](0.54,1.32)**	**0.83[c](0.40,1.26)**	**0.52[c](0.28,0.76)**	**0.45[b](0.19,0.70)**	0.10(-0.22,0.42)	-0.01(-0.34,0.33)	**0.30[c](0.08,0.51)**	**0.23[a](0.01,0.46)**
Increased frequency	-0.21(-0.50,0.08)	-0.19(-0.48,0.10)	0.03(-0.51,0.57)	-0.03(-0.60,0.53)	0.05(-0.33,0.44)	-0.02(-0.41,0.37)	**0.47[b](0.15,0.79)**	**0.43[a](0.10,0.75)**	-0.10(-0.39,0.19)	-0.08(-0.37,0.22)
Baseline psychological frailty	**0.58[c](0.49,0.67)**	**0.55[c](0.46,0.64)**	**0.59[c](0.47,0.72)**	**0.56[c](0.42,0.70)**	**0.46[c](0.36,0.56)**	**0.44[c](0.34,0.54)**	**0.57[c](0.46,0.67)**	**0.58[c](0.48,0.69)**	**0.54[c](0.46,0.63)**	**0.54[c](0.45,0.63)**
Age		0.01(-0.01,0.02)		-0.00(-0.03,0.03)		0.01(-0.02,0.03)		0.02(-0.01,0.04)		0.01(-0.00,0.03)
Sex										
Male		*Reference*		*Reference*		*Reference*		*Reference*		*Reference*
Female		0.04(-0.15,0.24)		0.05(-0.30,0.39)		**0.27[a](0.03,0.52)**		-0.02(-0.26,0.23)		0.10(-0.07,0.26)
Educational level										
Tertiary or higher		*Reference*		*Reference*		*Reference*		*Reference*		*Reference*
Secondary or equivalent		0.11(-0.20,0.42)		-0.19(-0.65,0.28)		0.14(-0.24,0.51)		0.14(-0.23,0.51)		-0.05(-0.33,0.23)
Primary or less versus		**0.31[a](0.02,0.60)**		0.02(-0.43,0.46)		-0.07(-0.67,0.52)		0.17(-0.27,0.61)		-0.28(-0.89,0.32)
Living situation										
Living with others		*Reference*		*Reference*		*Reference*		*Reference*		*Reference*

Supplementary Table S4 Multiple linear regression models (12-month change in moderate physical activity and psychological frailty) stratified by country (Continued)

Items	Spain 12-month follow-up Psychological frailty		Greece 12-month follow-up Psychological frailty		Croatia 12-month follow-up Psychological frailty		The Netherlands 12-month follow-up Psychological frailty		The United Kingdom 12-month follow-up Psychological frailty	
	Crude Model B(95%CI)	Adjusted Model B(95%CI)	Crude Model B(95%CI)	Adjusted Model B(95%CI)	Crude Model B(95%CI)	Adjusted Model B(95%CI)	Crude Model B(95%CI)	Adjusted Model B(95%CI)	Crude Model B(95%CI)	Adjusted Model B(95%CI)
Living alone		-0.08(-0.29,0.12)		0.01(-0.37,0.40)		-0.22(-0.44,0.00)		-0.15(-0.39,0.09)		-0.09(-0.26,0.07)
Smoking										
No		*Reference*		*Reference*		*Reference*		*Reference*		*Reference*
Yes		0.17(-0.21,0.54)		0.01(-0.41,0.43)		**0.41[a](0.01,0.81)**		0.08(-0.28,0.43)		-0.08(-0.39,0.24)
Alcohol risk										
No		*Reference*		*Reference*		*Reference*		*Reference*		*Reference*
Yes		-0.04(-0.23,0.16)		-0.31(-0.64,0.02)		-0.29(-0.58,0.00)		-0.02(-0.20,0.23)		0.00(-0.17,0.18)
Multi-morbidity										
No		*Reference*		*Reference*		*Reference*		*Reference*		*Reference*
*Yes **versus** no*		0.02(-0.26,0.31)		0.29(-0.24,0.83)		-0.18(-0.53,0.18)		0.10(-0.21,0.41)		0.14(-0.22,0.49)
Intervention condition										
Control group		*Reference*		*Reference*		*Reference*		*Reference*		*Reference*
Intervention group		0.13(-0.05,0.31)		-0.12(-0.43,0.19)		-0.19(-0.40,0.01)		-0.23(-0.45,0.00)		-0.04(-0.20,0.12)
Adjusted R square, %	35.7	36.4	44.5	44.4	25.6	27.7	33.2	33.2	30.9	30.4

[a] $p<0.05$, [b] $p<0.01$, [c] $p<0.001$, significant effect estimates in bold



Supplementary Figure S1 Frequency of moderate physical activity of participants
Three categories of frequency of physical activity; 'More than once a week'= (a) more than once a week; 'One a week or less'= (b) once a week and (c) one to three times a month; 'Never'= (d) hardly ever, or never.

4

Chapter 4

Reliability and validity of the Tilburg Frailty Indicator in 5 European countries

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ABSTRACT

Objectives To assess the internal consistency, convergent and divergent validity and concurrent validity of the Tilburg Frailty Indicator (TFI) within community-dwelling older people in Spain, Greece, Croatia, the Netherlands and the United Kingdom.

Design Cross-sectional study.

Setting Primary care and community settings.

Participants In total, 2250 community-dwelling older people (60.3% women; mean age = 79.7 years; SD = 5.7 years).

Methods We assessed the reliability and validity of the full TFI as well as its physical, psychological, and social domains. Baseline data of the Urban Health Centers Europe project were used. The internal consistency was assessed with the Cronbach alpha. The convergent and divergent validity were assessed using Pearson correlation coefficients between the domains and alternative measures: the 12-item short-form, Groningen activity restriction scale, 5-item mental well-being scale of the 36-Item Short Form Survey, and the De Jong Gierveld loneliness scale. The concurrent validity was assessed by the area under the receiver operating characteristic curve with physically frail (Survey of Health, Ageing and Retirement in Europe-Frailty Instrument), loss of independence (Groningen activity restriction scale), limited function (Global Activity Limitation Index), poor mental health (5-item mental well-being scale of the 36-Item Short Form Survey), and feeling lonely (De Jong Gierveld loneliness scale) as criteria.

Results The internal consistency of the full TFI was satisfactory with the Cronbach alpha ≥0.70 in the total population and in each country. The internal consistency of the psychological and social domains was not satisfactory. The convergent and divergent validity of the physical, psychological and social domains was supported by all the alternative measures in the total population and in each country. The concurrent validity of the full TFI and the physical, psychological and social domains was supported with most area under the receiver operating characteristic curve ≥0.70 in the total population and in each country.

Conclusions and Implications The TFI is a reliable and valid instrument to assess frailty in community-dwelling older people in Spain, Greece, Croatia, the Netherlands and the United Kingdom.

KEYWORDS Europe; Self-reported questionnaire; Frailty; Older people; Reliability; Validity

INTRODUCTION

With the population rapidly ageing worldwide and the increasing prevalence of chronic multimorbidity, frailty is increasingly recognized as a complex and important public health issue.[1, 2] People with frailty have a higher risk of various negative outcomes such as falls[3], disability[4], long-term care[5], hospitalization[4] and mortality[6]. To improve the management of frailty and deliver more patient-centered care, providing supportive care to people with frailty ideally starts with the identification of their severity level of frailty.[7]

Although many assessment tools to measure the severity level of frailty have been developed in the past decades[7, 8], there is no global standard assessment measure for frailty.[8] Hence, it is important to have robust data and studies on the psychometric properties including reliability and validity of existing instruments, in order to be able to compare and select the most appropriate and relevant health measurement tools.

Furthermore, researchers, health care professionals and policymakers increasingly acknowledge the multidimensional nature of frailty.[1, 5, 9] However, most frailty assessment measures only cover the physical domain [4, 10, 11], but not the psychological and social domains.[9]

The Tilburg Frailty Indicator (TFI) is a short self-reported questionnaire, originally developed for identifying frail community-dwelling older people in the Netherlands in 2010.[5, 12] It considers frailty from a bio-psycho-social framework, which includes 15 items addressing 3 domains: the physical, psychological and social domains.[12] Pialoux et al[13] found that the TFI is one of the best three measures for screening frailty in primary health care settings. The psychometric properties of the TFI have been extensively examined especially in Dutch populations.[9, 12, 14] However, the validity of the single domains of the TFI, especially the psychological and social domains, has not yet been extensively examined.[15-19]

In addition, research on the properties of the TFI among different populations are still lacking.[5] For example, the TFI has not yet been validated in Greece, Croatia or the United Kingdom (UK). Conducting the validation study in these countries contributes to the current literature with important evidence on psychometric properties of the TFI. Furthermore, reporting the results of the total population of the five European countries contributes to the generalizability of the results to other local contexts.

This study aims to assess the reliability and validity of the full TFI and its three domains in a population of community-dwelling older people from 5 European countries, including Spain, Greece, Croatia, the Netherlands and the UK. In addition, the reliability and validity will be assessed for each country separately.

We examined the following aspects: (1) the internal consistency (reliability) of the full TFI and the 3 domains; (2) the convergent and divergent validity (construct validity) of the 3 domains; and (3) the concurrent validity (criterion validity) of the full TFI and the 3 domains.

METHODS

Study Population and Data Collection

The Urban Health Centers Europe (UHCE) project aimed to promote the healthy ageing of older people by implementing a coordinated preventive care approach.[20, 21] The study design has been described in detail elsewhere.[20, 21] Citizens aged 70 years or older, who lived independently and were expected to be able to participate in the project for at least 6 months were eligible. Participants were recruited in primary care and community settings in 5 European countries between May 2015 and June 2017. Data was collected with a self-reported questionnaire in the local language at baseline and at 12-months follow-up. Ethical committee procedures have been followed in all countries, and approval has been provided.[20, 21] Written informed consent was obtained from all participants. The study was registered as ISRCTN52788952.

In the current study, we adopted a cross-sectional design and used baseline data of the UHCE project (2325 participants from 5 European countries).[20] Participants with missing data on 1 or more items of the TFI (n = 75) were excluded. Thus, our analyses included 2250 participants.

Measures

Frailty

The TFI contains 15 items addressing the physical, psychological and social domains.[12, 15, 22] The physical domain is assessed with 8 items regarding physical health, unexplained weight loss, difficulties in walking, balance, hand strength, physical tiredness, eyesight and hearing impairments. The psychological domain is assessed with 4 items regarding problems with memory, feeling down, feeling nervous or anxious and inability to cope with problems. The social domain is assessed with 3 items regarding living alone, lack of social relationships and lack of social support. Eleven items have 2 response categories: Yes and No; and 4 items have 3 response categories: Yes, Sometimes and No.[5] All items were dichotomized after recoding and scored with 0 or 1 point.[5, 19] The score range of the full TFI is 0-15, that of the physical domain 0-8, psychological domain 0-4 and social domain 0-3.[5] A detailed description of the recoding is provided in Supplementary Table S1.

Previously validated versions of the TFI were available in Spanish[19], Dutch,[12] and English.[12] Because no validated translation of the TFI was available in Greek and Croatian, all items of the TFI were translated forward and backward.[20, 21] Forward- and back-translations were discussed by the study team, and the translation was adapted when needed. Each language version of the TFI was piloted in at least five older people in the respective countries. Misinterpretation of questions were identified and minor changes were made.[20] The translations of the TFI in the five languages are provided in Supplementary Table S2.

Other measures

Health-Related Quality of Life (HRQoL) was measured with the 12-item short-form (SF-12) which contains 12 questions covering 8 health domains. The 8 domains are summarized in

the Physical Component Summary (PCS) and Mental Component Summary (MCS), both ranging from 0 (lowest) to 100 (highest level of health).[23]

Activity restriction was measured with the Groningen Activity Restriction Scale (GARS) which contains 18 items on independence of activities of daily living (GARS-ADL; 11 items) and instrumental ADL (GARS-IADL; 7 items).[24] The GARS score ranges from 18 (highest) to 72 (lowest level of independence) and the GARS–ADL score from 11 (highest) to 44 (lowest level of independence). Participants with a GARS score ≥29 were categorized as experiencing a loss of independence.[24]

Mental well-being was measured with the full 5-item mental well-being scale of the 36-Item Short Form Survey (MHI-5) which measures nervousness, downheartedness and feeling sad, jollity, calmness and happiness (score range: 0-100).[25, 26] Participants with a MHI-5 score ≤52 were categorized as showing signs of poor mental health.[25]

Loneliness was measured with the short 6-item version of the De Jong Gierveld loneliness scale (short-JG) which contains 2 domains: emotional (3 items) and social loneliness (3 items).[27] The overall loneliness score ranges from 0-6 and the domain scores from 0-3, with higher scores indicating a higher experience of loneliness. Participants with a short-JG score ≥ 2 were categorized as feeling lonely.

Physical frailty was additionally assessed with the Survey of Health, Ageing and Retirement in Europe-Frailty Instrument (SHARE-FI) which contains 5 items: exhaustion, weight loss, slowness, physical activity and hand-grip strength.[28, 29] An estimation of a discrete factor model based on the 5 items determined whether participants were physically frail.[28]

Activity limitation was measured with the 1-item Global Activity Limitation Index (GALI). Participants who indicated their function to be moderately or severely limited were categorised as having a limited function.[30, 31]

Socio-demographic factors

Age (in years), sex, level of education, living situation (living alone/not living alone) were assessed. The level of education concerned the highest level of education the participant completed and was categorized according to the 2011 International Standard Classification of Education (ISCED)[32] into primary or less (ISCED 0-1), secondary or equivalent (2-5) and tertiary or higher (6-8).

Statistical Analyses

Scale scores were described by conventional descriptive statistics.[33] We applied the framework used by Gobbens et al[7] who originally developed the TFI for the evaluation of the internal consistency and specific aspects of the validity of the TFI. The internal consistency was assessed with the Cronbach alpha; a value of the Cronbach alpha between 0.7 to 0.9 was considered as a satisfactory internal consistency.[34] To examine the convergent and divergent validity, we hypothesized that the SF-12 PCS, GARS and GARS-ADL strongly relate to the

physical domain of the TFI and less the other 2 domains. We hypothesized that the SF-12 MCS and MHI-5 strongly relate to the psychological domain of the TFI and less the other 2. We also hypothesized that the short-JG strongly relates to the social domain of the TFI and less to the other 2. The convergent and divergent validity were assessed using Pearson correlation coefficients.[12] A statistically significant correlation between a domain score and the score of an alternative measure of the same domain was considered as a satisfactory convergent validity; with a higher correlation indicating a better validity.[12, 15, 22] Divergent validity was assumed if each alternative measure had a higher correlation with the corresponding domain of the TFI, but a lower correlation with the each of the other domains of the TFI.[12, 15, 22] To examine the concurrent validity, we used the following alternative measures as the criterion: (1) SHARE-FI, (2) GARS and (3) GALI (physical domain), (4) MHI-5 (psychological domain) and (5) short-JG (social domain). The concurrent validity was assessed using the receiver operating characteristic (ROC) curve analysis.[12, 22] Accuracy was measured by the area under the ROC curve (AUC). An AUC between 0.7 and 0.8 was considered acceptable, between 0.8 and 0.9 excellent and an AUC of more than 0.9 was considered outstanding.[35] The Youden index (sensitivity + specificity - 1) was adopted as the criterion for selecting the optimum cut-off point(s).[36]

All analyses were conducted among the total population as well as by country. All analyses were performed with SPSS v 23.0 (IBM SPSS Statistics for Windows, Armonk, NY). The level of significance was *P*-value <0.05.

RESULTS

Participant Characteristics

Table 1 presents the general characteristics of the total population and by country. The mean age of the total population was 79.7 (standard deviation = 5.7) years and 60.3% were women. Participants from Spain and Greece were younger, had less often completed secondary education and less often lived alone than other countries ($P < .001$). Participants from Croatia have higher physical and social domain scores than other countries, and participants from Greece have higher psychological domain scores ($P < .001$).

Scoring Distributions

Table 2 presents the score distributions the TFI. A floor effect (>25% of the respondents had the lowest possible score[37]) was observed in the physical (the Netherlands), psychological (the total population, Spain, the Netherlands and the UK) and social (the total population and each country except Croatia) domains.

Table 1 Characteristics of the participants, frailty assessed with the Tilburg Frailty Indicator, outcomes of alternative measures (n=2250)

Characteristic	Total (n=2250)	Participants from each individual country					
		Spain (n=496)	Greece (n=354)	Croatia (n=476)	NL (n=366)	UK (n=558)	*P*-Value
Basic characteristics							
Age‡	79.7±5.7	**77.5±5.2**	**75.3±5.4**	**81.3±4.5**	**81.5±5.3**	**81.9±5.1**	*P* <.001*
Women	1354(60.3)	**311(62.8)**	**185(52.6)**	**326(68.5)**	223(60.9)	**309(55.4)**	*P* <.001†
Level of education							*P* <.001†
Primary or less	608(27.3)	**325(65.5)**	**173(51.2)**	**18(3.8)**	**82(22.9)**	**10(1.8)**	
Secondary	1386(62.3)	**120(24.2)**	**118(34.9)**	**400(84.0)**	**249(69.6)**	**499(89.7)**	
Tertiary	230(10.3)	51(10.3)	**47(13.9)**	58(12.2)	27(7.5)	47(8.5)	
Living alone	859(38.3)	**144(29.1)**	**72(20.5)**	192(40.3)	**172(47.0)**	**279(50.2)**	*P* <.001†
Frailty assessed with the TFI‡							
Full TFI score (score range 0-15)	5.20±3.17	**4.64±2.88**	**5.80±3.09**	**6.92±3.20**	**4.25±3.01**	**4.47±2.91**	*P* <.001*
Physical domain (0-8)	3.00±2.14	**2.74±1.88**	3.01±2.08	**4.24±2.19**	**2.39±2.08**	**2.59±1.98**	*P* <.001*
Poor physical health (0-1)	0.34±0.47	**0.27±0.44**	0.36±0.48	**0.54±0.50**	0.33±0.47	**0.23±0.42**	*P* <.001*
Unexplained weight loss (0-1)	0.11±0.31	**0.07±0.26**	0.11±0.31	**0.18±0.38**	**0.07±0.25**	0.10±0.31	*P* <.001*
Difficulty in walking (0-1)	0.54±0.50	**0.42±0.49**	0.55±0.50	**0.75±0.44**	**0.44±0.50**	0.54±0.50	*P* <.001*
Difficulty in maintaining balance (0-1)	0.39±0.49	**0.32±0.47**	0.36±0.48	**0.52±0.50**	**0.33±0.47**	0.41±0.49	*P* <.001*
Poor hearing (0-1)	0.38±0.49	0.40±0.49	0.40±0.49	**0.45±0.50**	**0.32±0.47**	**0.34±0.47**	*P* <.001*
Poor vision (0-1)	0.38±0.49	**0.33±0.47**	0.38±0.49	**0.72±0.45**	**0.25±0.43**	**0.21±0.41**	*P* <.001*
Hand strength (0-1)	0.36±0.48	0.40±0.49	0.32±0.47	**0.48±0.50**	**0.23±0.42**	0.34±0.47	*P* <.001*
Physical tiredness (0-1)	0.50±0.50	0.53±0.50	0.54±0.50	**0.60±0.49**	**0.42±0.49**	**0.41±0.49**	*P* <.001*
Psychological domain (0-4)	1.18±1.07	1.11±1.03	**1.68±1.16**	**1.47±1.06**	**0.81±0.97**	**0.91±0.92**	*P* <.001*
Problems with memory (0-1)	0.13±0.34	0.14±0.34	**0.20±0.40**	**0.10±0.30**	**0.09±0.28**	0.14±0.34	*P* <.001*
Feeling down (0-1)	0.50±0.50	0.47±0.50	**0.57±0.50**	**0.64±0.48**	**0.38±0.49**	**0.45±0.50**	*P* <.001*
Feeling nervous or anxious (0-1)	0.45±0.50	0.45±0.50	**0.69±0.46**	**0.62±0.49**	**0.25±0.43**	**0.28±0.45**	*P* <.001*
Inability to cope with problems (0-1)	0.10±0.30	**0.05±0.23**	**0.21±0.41**	0.12±0.32	0.10±0.29	**0.05±0.22**	*P* <.001*
Social domain (0-3)	1.01±0.89	**0.79±0.85**	**1.10±0.86**	**1.20±0.89**	1.05±0.95	0.97±0.85	*P* <.001*
Living alone (0-1)	0.39±0.49	**0.28±0.45**	**0.21±0.41**	0.41±0.49	**0.48±0.50**	**0.51±0.50**	*P* <.001*

Table 1 Characteristics of the participants, frailty assessed with the Tilburg Frailty Indicator, outcomes of alternative measures (n=2250) (Contined)

Characteristic	Total (n=2250)	Participants from each individual country					
		Spain (n=496)	Greece (n=354)	Croatia (n=476)	NL (n=366)	UK (n=558)	*P*-Value
Social relationships (0-1)	0.44±0.50	**0.35±0.48**	**0.57±0.50**	**0.57±0.50**	**0.37±0.48**	**0.37±0.48**	*P* <.001*
Social support (0-1)	0.19±0.39	**0.16±0.37**	**0.32±0.47**	**0.23±0.42**	0.21±0.41	**0.09±0.28**	*P* <.001*
Other scores (alternative measures) (score range)‡							
HRQoL PCS score (SF-12) (0-100)	41.86±12.07	**45.62±11.03**	**44.31±12.07**	**37.83±11.30**	41.41±12.58	**40.67±12.04**	*P* <.001*
HRQoL MCS score (SF-12) (0-100)	50.28±10.67	**52.17±11.09**	**48.95±9.64**	**44.61±11.09**	**54.21±9.90**	**51.84±8.75**	*P* <.001*
Activities restriction score (GARS) (18-72)	25.30±9.72	**22.12±6.95**	**23.31±7.73**	**30.48±12.78**	25.80±8.69	24.65±8.77	*P* <.001*
Activities of daily living restriction score (GARS - ADL) (11-44)	14.76±4.95	**13.13±3.48**	**13.73±3.55**	**17.50±6.90**	14.61±4.27	14.60±4.23	*P* <.001*
Mental well-being score (MHI-5) (0-100)	73.98±20.67	75.10±21.73	**64.16±18.94**	**62.92±20.26**	**81.98±16.45**	**83.31±15.97**	*P* <.001*
Loneliness score (short-JG) (0-6)	1.79±1.75	**1.46±1.60**	**2.05±1.71**	**2.87±1.82**	**1.46±1.74**	**1.21±1.37**	*P* <.001*
Adverse outcomes (alternative measures)							
Physical frailty (SHARE-FI)	477(21.5)	**69(14.1)**	**63(18.4)**	103(22.1)	80(22.2)	**162(29.3)**	*P* <.001†
Loss of independence (GARS)	580(25.8)	**62(12.5)**	**61(17.4)**	**211(44.3)**	**116(31.8)**	130(23.3)	*P* <.001†
Limited function (GALI)	1190(53.1)	**184(37.1**)	169(48.4)	**324(68.4**)	177(48.5)	**336(60.2)**	*P* <.001†
Poor mental health (MHI-5)	320(14.4)	68(13.8)	**74(21.4)**	**133(28.1)**	**18(4.9)**	**27(4.9)**	*P* <.001†
Feeling lonely (short-JG)	1033(46.5)	**183(37.1)**	**187(53.6)**	**349(73.8)**	**138(38.0)**	**176(32.3)**	*P* <.001†

TFI, Tilburg Frailty Indicator; HRQoL, Health-Related Quality of Life; SF-12, 12-item Short form; PCS, Physical Component Summary summarized by the SF-12; MCS, Mental Component Summary summarized by the SF-12; GARS, 18-item Groningen Activity Restriction Scale; GARS-ADL, 11-item subscale of the 18-item Groningen Activity Restriction Scale to measure independence of Activities Of Daily Living; MHI-5, full 5-item mental well-being scale of the 36-Item Short Form Survey; short-JG, 6-item version of the De Jong Gierveld loneliness scale; SHARE-FI, Survey of Health, Ageing and Retirement in Europe-Frailty Instrument; NL, the Netherlands; UK, the United Kingdom.
Missing items: Women = 3; Level of education = 26; Living alone = 6; SF-12 = 112; GARS = 4; GARS - ADL = 5; short-JG = 27; MHI-5 = 22; SHARE-FI = 36; GALI = 8
Presented as mean±SD or N(%)

* *P*-value based on ANOVA;

† *P*-value based on Chi-square test; Post-hoc testing was performed after a statistically significant chi-squared test; *P*-value<0.05 in bold

‡ The mean of each country was compared with the mean of the other four countries with a respective independent *t* test; *P*-value<0.05 in bold

Internal Consistency

Table 2 presents the internal consistency of the TFI. The Cronbach alpha of the full TFI and the physical, psychological and social domains was 0.74, 0.70, 0.52 and 0.29 respectively in the total population. The Cronbach alpha of the full TFI was ≥0.70 in each country. The Cronbach alpha of the physical domain was >0.70 in Croatia and the Netherlands, but varied between 0.60 and 0.68 in the other 3 countries. The Cronbach alpha of the psychological domain varied between 0.38 and 0.55 and that of the social domain between 0.22 and 0.43.

Convergent and Divergent Validity

Table 3 presents the convergent and divergent validity of the TFI domains. In the total population and in each country, the physical domain correlated significantly with the SF-12 PCS, GARS and GARS-ADL. These correlations were higher than those between the psychological or social domain versus the SF-12 PCS, GARS and GARS–ADL, respectively.

In the total population and in each country, the psychological domain correlated significantly with the SF-12 MCS and MHI-5. These correlations were higher than those between the physical or social domain versus the SF-12 MCS and MHI-5, respectively.

In the total population and in each country, the social domain correlated significantly with the short-JG. These correlations were higher than those between the physical or psychological domain and the short-JG.

Concurrent Validity

Table 4 presents the concurrent validity of the TFI and its 3 domains.

In the total population and in each country, the AUCs of the full TFI and the physical domain using physically frail or loss of independence as the criterion were excellent and using limited function as the criterion were acceptable to excellent.

In the total population and in most of the countries, the AUCs of the full TFI and the psychological domain using poor mental health as the criterion were excellent. In Greece, the AUCs of the full TFI and the psychological domain were acceptable.

In the total population and in most of the countries, the AUCs of the full TFI and the social domain using feeling lonely as the criterion were acceptable. In Croatia, the AUC of the social domain was not acceptable.

Table 2 Score distributions and internal consistency of the TFI (n=2250)

TFI	Population	Mean score±SD	Range	% of Min*	% of Max†	25th % tile	50th %tile‡	75th %tile	Cronbach alpha§
Full TFI (15 items)	**Total**	5.20±3.17	0-14	5.0	0.2	3	5	7	**0.74**
	Spain	4.64±2.88	0-13	3.6	0.2	2	4	7	**0.70**
	Greece	5.80±3.09	0-14	3.1	0.3	4	6	8	**0.72**
	Croatia	6.92±3.20	0-14	1.5	0.8	4	7	9	**0.75**
	The Netherlands	4.25±3.01	0-13	10.1	0.5	2	4	7	**0.74**
	The United Kingdom	4.47±2.91	0-13	7.2	0.2	2	4	6	**0.72**
Physical domain (8 items)	**Total**	3.00±2.14	0-8	14.0	1.2	1	3	5	**0.70**
	Spain	2.74±1.88	0-8	11.7	0.4	1	2	4	0.60
	Greece	3.01±2.08	0-8	12.4	0.8	1	3	5	0.68
	Croatia	4.24±2.19	0-8	4.6	3.4	2	4	6	**0.72**
	The Netherlands	2.39±2.08	0-8	26.0	0.5	0	2	4	**0.73**
	The United Kingdom	2.59±1.98	0-8	17.4	0.5	1	2	4	0.67
Psychological domain (4 items)	**Total**	1.18±1.07	0-4	34.4	2.0	0	1	2	0.52
	Spain	1.11±1.03	0-4	35.5	1.8	0	1	2	0.49
	Greece	1.68±1.16	0-4	19.2	5.4	1	2	3	0.55
	Croatia	1.47±1.06	0-4	24.8	2.7	1	2	2	0.55
	The Netherlands	0.81±0.97	0-4	49.2	1.1	0	1	1	0.50
	The United Kingdom	0.91±0.92	0-4	41.4	0.2	0	1	2	0.38
Social domain (3 items)	**Total**	1.01±0.89	0-3	33.4	5.4	0	1	2	0.29
	Spain	0.79±0.85	0-3	45.0	4.0	0	1	1	0.33
	Greece	1.10±0.86	0-3	27.1	5.1	0	1	2	0.22
	Croatia	1.20±0.89	0-3	23.1	8.2	1	1	2	0.24
	The Netherlands	1.05±0.95	0-3	36.1	6.8	0	1	2	0.43
	The United Kingdom	0.97±0.85	0-3	34.2	3.4	0	1	2	0.33

TFI, Tilburg Frailty Indicator

* Percentage of respondents with the lowest possible score (floor); † Percentage of respondents with the highest possible score (ceiling); ‡ Median.

§ A value of Cronbach alpha between 0.7 to 0.9 represented satisfactory internal consistency reliability[34]; The value of Cronbach alpha ≥0.7 in bold.

Table 3 Convergent and divergent validity: correlations of frailty domains with the alternative measures (n=2250)

Domain	Score of alternative measures	Population	Full TFI score		Physical domain score		Psychological domain score		Social domain score	
			r	*P*-value*	*r*†	*P*-value*	*r*†	*P*-value*	*r*†	*P*-value*
Physical domain	**HRQoL PCS score (SF-12)**	**Total**	-0.556	*P* <.001	**-0.618**	*P* <.001	-0.251	*P* <.001	-0.195	*P* <.001
		Spain	-0.537	*P* <.001	**-0.621**	*P* <.001	-0.250	*P* <.001	-0.136	*P* =0.001
		Greece	-0.553	*P* <.001	**-0.599**	*P* <.001	-0.244	*P* <.001	-0.219	*P* <.001
		Croatia	-0.593	*P* <.001	**-0.610**	*P* <.001	-0.353	*P* <.001	-0.206	*P* <.001
		The Netherlands	-0.590	*P* <.001	**-0.693**	*P* <.001	-0.166	*P* =0.001	-0.191	*P* <.001
		The United Kingdom	-0.570	*P* <.001	**-0.624**	*P* <.001	-0.315	*P* <.001	-0.139	*P* =0.001
	Activities restriction score (GARS)	**Total**	0.568	*P* <.001	**0.588**	*P* <.001	0.339	*P* <.001	0.203	*P* <.001
		Spain	0.545	*P* <.001	**0.555**	*P* <.001	0.363	*P* <.001	0.177	*P* <.001
		Greece	0.564	*P* <.001	**0.577**	*P* <.001	0.338	*P* <.001	0.177	*P* <.001
		Croatia	0.572	*P* <.001	**0.584**	*P* <.001	0.392	*P* <.001	0.155	*P* <.001
		The Netherlands	0.600	*P* <.001	**0.607**	*P* <.001	0.277	*P* <.001	0.286	*P* <.001
		The United Kingdom	0.539	*P* <.001	**0.562**	*P* <.001	0.375	*P* <.001	0.125	*P* =0.001
	Activities of daily living restriction score (GARS - ADL)	**Total**	0.560	*P* <.001	**0.580**	*P* <.001	0.327	*P* <.001	0.209	*P* <.001
		Spain	0.544	*P* <.001	**0.566**	*P* <.001	0.348	*P* <.001	0.168	*P* <.001
		Greece	0.553	*P* <.001	**0.547**	*P* <.001	0.326	*P* <.001	0.223	*P* <.001
		Croatia	0.565	*P* <.001	**0.578**	*P* <.001	0.379	*P* <.001	0.161	*P* <.001
		The Netherlands	0.590	*P* <.001	**0.597**	*P* <.001	0.255	*P* <.001	0.299	*P* <.001
		The United Kingdom	0.531	*P* <.001	**0.552**	*P* <.001	0.365	*P* <.001	0.134	*P* =.001
Psychological domain	**HRQoL MCS score (SF-12)**	**Total**	-0.553	*P* <.001	-0.421	*P* <.001	**-0.560**	*P* <.001	-0.283	*P* <.001
		Spain	-0.480	*P* <.001	-0.297	*P* <.001	**-0.569**	*P* <.001	-0.276	*P* <.001
		Greece	-0.504	*P* <.001	-0.357	*P* <.001	**-0.553**	*P* <.001	-0.204	*P* <.001
		Croatia	-0.623	*P* <.001	-0.509	*P* <.001	**-0.579**	*P* <.001	-0.291	*P* <.001
		The Netherlands	-0.450	*P* <.001	-0.267	*P* <.001	**-0.493**	*P* <.001	-0.336	*P* <.001
		The United Kingdom	-0.430	*P* <.001	-0.313	*P* <.001	**-0.480**	*P* <.001	-0.207	*P* <.001

Table 3 Convergent and divergent validity: correlations of frailty domains with the alternative measures (n=2250) (Continued)

Domain	Score of alternative measures	Population	Full TFI score		Physical domain score		Psychological domain score		Social domain score	
			r	*P*-value*	*r*†	*P*-value*	*r*†	*P*-value*	*r*†	*P*-value*
Psychological domain	**Mental well-being score (MHI-5)**	**Total**	-0.648	*P* <.001	-0.496	*P* <.001	**-0.659**	*P* <.001	-0.325	*P* <.001
		Spain	-0.612	*P* <.001	-0.437	*P* <.001	**-0.636**	*P* <.001	-0.337	*P* <.001
		Greece	-0.564	*P* <.001	-0.411	*P* <.001	**-0.571**	*P* <.001	-0.269	*P* <.001
		Croatia	-0.671	*P* <.001	-0.540	*P* <.001	**-0.632**	*P* <.001	-0.331	*P* <.001
		The Netherlands	-0.581	*P* <.001	0.365	*P* <.001	**-0.634**	*P* <.001	-0.392	*P* <.001
		The United Kingdom	-0.598	*P* <.001	-0.452	*P* <.001	**-0.644**	*P* <.001	-0.279	*P* <.001
Social domain	**Loneliness score (short-JG)**	**Total**	0.579	*P* <.001	0.404	*P* <.001	0.478	*P* <.001	**0.521**	*P* <.001
		Spain	0.511	*P* <.001	0.313	*P* <.001	0.469	*P* <.001	**0.471**	*P* <.001
		Greece	0.504	*P* <.001	0.312	*P* <.001	0.395	*P* <.001	**0.522**	*P* <.001
		Croatia	0.517	*P* <.001	0.339	*P* <.001	0.453	*P* <.001	**0.483**	*P* <.001
		The Netherlands	0.569	*P* <.001	0.334	*P* <.001	0.437	*P* <.001	**0.622**	*P* <.001
		The United Kingdom	0.551	*P* <.001	0.372	*P* <.001	0.460	*P* <.001	**0.514**	*P* <.001

TFI, Tilburg Frailty Indicator; HRQoL, Health-Related Quality of Life; SF-12, 12-item Short form; PCS, Physical Component Summary summarized by the SF-12; MCS, Mental Component Summary summarized by the SF-12; GARS, 18-item Groningen Activity Restriction Scale; GARS - ADL, 11-item subscale of the 18-item Groningen Activity Restriction Scale to measure independence of Activities Of Daily Living; MHI-5, full 5-item mental well-being scale of the 36-Item Short Form Survey; short-JG, 6-item version of the De Jong Gierveld loneliness scale

Missing items: SF-12 = 112; GARS = 4; GARS - ADL = 5; MHI-5 = 22; short-JG = 27

* One-tailed *P* value.

† Highest value of Pearson correlation coefficient in the three domains of frailty in bold.

Table 4 Concurrent validity of the TFI and its three domains (n=2250)

Adverse outcomes (measures)	Screening	Population	Cut-off Point*	Sensitivity	Specificity	AUC (95% CI)†
Physically frail (SHARE-FI)	**Full TFI**	**Total**	≥6	0.80	0.66	**0.81(0.79, 0.83)**
			≥7	0.69	0.76	
		Spain	≥6	0.80	0.71	**0.84(0.79, 0.89)**
		Greece	≥9	0.67	0.90	**0.87(0.83, 0.92)**
		Croatia	≥8	0.82	0.66	**0.81(0.76, 0.85)**
		The Netherlands	≥6	0.76	0.78	**0.84(0.79, 0.89)**
		The United Kingdom	≥5	0.84	0.68	**0.84(0.80, 0.87)**
	Physical domain	**Total**	≥4	0.77	0.70	**0.81(0.79, 0.83)**
		Spain	≥4	0.75	0.72	**0.82(0.77, 0.87)**
		Greece	≥5	0.67	0.82	**0.84(0.78, 0.89)**
		Croatia	≥6	0.71	0.78	**0.80(0.75, 0.84)**
		The Netherlands	≥4	0.76	0.83	**0.85(0.81, 0.90)**
		The United Kingdom	≥3	0.84	0.68	**0.83(0.80, 0.87)**
Loss of independence (GARS)	**Full TFI**	**Total**	≥6	0.82	0.69	**0.83(0.82, 0.85)**
		Spain	≥6	0.89	0.72	**0.87(0.83, 0.91)**
		Greece	≥8	0.69	0.79	**0.81(0.75, 0.87)**
		Croatia	≥8	0.74	0.79	**0.84(0.81, 0.88)**
		The Netherlands	≥5	0.82	0.76	**0.86(0.82, 0.90)**
		The United Kingdom	≥5	0.84	0.64	**0.82(0.78, 0.86)**
	Physical domain	**Total**	≥4	0.80	0.74	**0.84(0.83, 0.86)**
		Spain	≥4	0.89	0.74	**0.88(0.83, 0.92)**
		Greece	≥5	0.66	0.82	**0.83(0.77, 0.88)**
		Croatia	≥5	0.79	0.73	**0.84(0.81, 0.88)**
		The Netherlands	≥4	0.69	0.88	**0.85(0.80, 0.89)**
		The United Kingdom	≥4	0.70	0.80	**0.84(0.80, 0.87)**

Table 4 Concurrent validity of the TFI and its three domains (n=2250) (Continued)

Adverse outcomes (measures)	Screening	Population	Cut-off Point*	Sensitivity	Specificity	AUC (95% CI)†
Limited function (GALI)	**Full TFI**	**Total**	≥5	0.76	0.69	**0.80(0.78, 0.81)**
		Spain	≥5	0.77	0.67	**0.79(0.75, 0.83)**
		Greece	≥6	0.70	0.68	**0.74(0.69, 0.79)**
		Croatia	≥7	0.74	0.84	**0.86(0.83, 0.90)**
		The Netherlands	≥4	0.79	0.72	**0.82(0.78, 0.86)**
		The United Kingdom	≥4	0.74	0.70	**0.78(0.75, 0.82)**
	Physical domain	**Total**	≥3	0.76	0.70	**0.80(0.78, 0.82)**
		Spain	≥4	0.63	0.83	**0.80(0.76, 0.84)**
		Greece	≥3	0.75	0.64	**0.73(0.68, 0.78)**
		Croatia	≥4	0.81	0.77	**0.85(0.81, 0.89)**
		The Netherlands	≥2	0.84	0.68	**0.83(0.79, 0.88)**
		The United Kingdom	≥3	0.65	0.80	**0.80(0.77, 0.84)**
Poor mental health (MHI-5)	**Full TFI**	**Total**	≥7	0.78	0.74	**0.85(0.83, 0.87)**
		Spain	≥6	0.84	0.72	**0.85(0.81, 0.90)**
		Greece	≥6	0.85	0.58	**0.78(0.73, 0.84)**
			≥7	0.72	0.70	
		Croatia	≥9	0.74	0.80	**0.83(0.79, 0.87)**
		The Netherlands	≥6	0.83	0.68	**0.82(0.71, 0.93)**
			≥8	0.67	0.85	
		The United Kingdom	≥7	0.82	0.79	**0.87(0.81, 0.93)**
	Psychological domain	**Total**	≥2	0.91	0.70	**0.84(0.82, 0.86)**
		Spain	≥2	0.93	0.73	**0.85(0.80, 0.89)**
		Greece	≥2	0.89	0.52	**0.76(0.70, 0.81)**
		Croatia	≥2	0.93	0.59	**0.80(0.76, 0.84)**
		The Netherlands	≥2	0.78	0.81	**0.85(0.76, 0.94)**
		The United Kingdom	≥2	0.96	0.77	**0.90(0.86, 0.94)**

Table 4 Concurrent validity of the TFI and its three domains (n=2250) (Continued)

Adverse outcomes (measures)	Screening	Population	Cut-off Point*	Sensitivity	Specificity	AUC (95% CI)†
Feeling lonely (short-JG)	**Full TFI**	**Total**	≥6	0.66	0.76	**0.79(0.77, 0.81)**
		Spain	≥6	0.59	0.78	**0.75(0.71, 0.80)**
		Greece	≥7	0.55	0.81	**0.74(0.69, 0.79)**
		Croatia	≥8	0.54	0.81	**0.73(0.68, 0.77)**
		The Netherlands	≥5	0.73	0.77	**0.84(0.80, 0.88)**
		The United Kingdom	≥5	0.79	0.69	**0.79(0.75, 0.84)**
	Social domain	**Total**	≥2	0.60	0.79	**0.74(0.72, 0.76)**
		Spain	≥2	0.61	0.78	**0.74(0.70, 0.79)**
		Greece	≥2	0.73	0.64	**0.71(0.66, 0.77)**
		Croatia	≥2	0.65	0.69	0.69(0.64, 0.75)
		The Netherlands	≥1	0.75	0.64	**0.73(0.68, 0.79)**
		The United Kingdom	≥1	0.86	0.55	**0.76(0.71, 0.80)**

AUC, area under ROC curve; ROC, receiver operating characteristic; CI, confidential interval; TFI, Tilburg Frailty Indicator; SHARE-FI, Survey of Health, Ageing and Retirement in Europe-Frailty Instrument; GARS, 18-item Groningen Activity Restriction Scale; GALI, Global Activity Limitation Index; MHI-5, full 5-item mental well-being scale the 36-Item Short Form Survey; short-JG, 6-item version of the De Jong Gierveld loneliness scale

Missing items: SHARE-FI = 36; GARS = 4; GALI = 8; MHI-5 = 22; short-JG = 27

* The Youden index was adopted as the criterion for selecting the optimum cut-off point; if more than one cut-off points had the maximum value, all potential cut-off points as well as corresponding sensitivity and specificity were provided.

† 0.7≤AUC<0.8 is considered acceptable concurrent validity; 0.8≤AUC<0.9 excellent; AUC≥0.9 outstanding; The value of AUC≥0.7 in bold.

DISCUSSION

In the present study, within a diverse community-based sample of older people in Spain, Greece, Croatia, the Netherlands and the UK, we found an internal consistency of the full TFI and the physical domain in the total population and in each country. However, the internal consistency of the psychological and social domains was not satisfactory. Our results further support the convergent and divergent validity of the 3 domains in the total population and in each country. The concurrent validity of the full TFI and the 3 domains were supported in the total population and in each country, except for the social domain in Croatia.

Regarding the full TFI, the reliability was satisfactory with an internal consistency of the Cronbach alpha ≥0.70 in the total population and in each country. Previous studies in the Netherlands,[12] Portugal,[16] Poland,[18] Brazil,[15] and China[22] found similar results. The concurrent validity was acceptable with most AUCs ≥0.70 in the total population and in each country. This finding was similar to previous studies on the full TFI in the Netherlands,[12] Italy,[38] and China[22].

Regarding the physical domain, the internal consistency was satisfactory in the total population and in Croatia and the Netherlands, which was consistent with previous studies.[12, 15, 16, 18, 22] The Cronbach alpha of the physical domain in Spain, Greece and the UK varied between 0.60 and 0.67. Earlier studies in Germany,[17] Italy,[38] and Spain[19] reported similar results and concluded that the internal consistency was acceptable with the Cronbach alpha ≥0.60. The convergent and divergent validity was supported in the total population and in each country, which was consistent with previous studies.[12, 17, 22, 38] The concurrent validity was acceptable in the total population and in each country, which was consistent with previous studies on the physical domain in the Netherlands,[12] Italy,[38] and China[22].

Regarding the psychological and social domains, the internal consistency was satisfactory in none of the countries with the Cronbach alpha varying between 0.22 and 0.55. Previous studies reported similar findings.[12, 15, 16, 18, 22] The low internal consistency for the psychological and social domains might be caused by their small number of items.[12, 15] The Cronbach alpha increases with number of items. Therefore, adding items to the psychological and social domains would be beneficial, for instance items referring to feelings of insecurity and the number of social contacts.[5] In addition, the low Cronbach alpha values do not imply that the items of the psychological and (especially) social domains are invalid, but rather they function more as an index rather than as a scale. The convergent and divergent validity was supported in the total population and in each country. The concurrent validity of the psychological domain was acceptable in the total population and in each country and that of the social domain acceptable in all countries except Croatia. We recommend further studies on the social domain in Croatia, for instance, cultural adaptation of the items in the social domain. A previous study in China also reported an acceptable concurrent validity of the

psychological and social domains.[22] However, the reliability and validity of the psychological and social domains have otherwise received little attention in research before.

To the best of our knowledge, this is the first study to report the reliability and validity of the TFI for multiple European countries simultaneously and the first in Greece, Croatia and the UK. We investigated the validity of the full TFI and its three domains. However, some limitations of our study should be highlighted. First, we did not assess the consistency of the TFI over time (test-retest reliability). However, frailty is not assumed to be stable over time and a low test-retest correlation over the follow up period (12 months) may be expected. Therefore, we believe that assessing the consistency of the TFI across items (internal consistency) is sufficiently adequate for the current study. Second, we did not assess the sociocultural and language differences in the interpretation of individual items between countries. Consequently, we may have observed some unintended variation between countries. Still, we have paid specific attention to translating the items of the TFI for which no validated translation was available (Greece, Croatia). Further studies on the cultural adaption of the items are needed to confirm our findings. Third, most of the alternative measures chosen to examine convergent and divergent validity and concurrent validity have been widely applied by previous studies. However, there is no golden standard of choosing alternative measures of the TFI, and the number of alternative measures for psychological and social domains was limited by the data availability of the UHCE project. Further studies with more alternative measures are still needed. Finally, the application of the TFI in clinical practice still needs further study due to the absence of general population norms or reference scores,[9] and further research on the use of the TFI in other settings such as the hospital setting is still required.

CONCLUSIONS AND IMPLICATIONS

In summary, our study supported the reliability and validity of the full TFI and physical domain. The TFI may be applied as an instrument to assess frailty in community-dwelling older people for large-scale population studies on frailty in the five European countries. However, our conclusions are drawn from statistical methods, and we cannot prove whether the use of the TFI will lead to clinically meaningful outcomes. The reliability and validity of the psychological and social domains have not been studied extensively before and more investigations in different countries are needed in the future.

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Supplementary Table S1 Recoding of items in The Tilburg Frailty Indicator (TFI)

Items of TFI	Answer scoring		
Item 1 physical health	Yes=0	No=1	
Item 2 unexplained weight loss	Yes=1	No=0	
Item 3 difficulties in walking	Yes=1	No=0	
Item 4 difficulties in maintaining balance	Yes=1	No=0	
Item 5 poor hearing	Yes=1	No=0	
Item 6 poor eyesight	Yes=1	No=0	
Item 7 hand strength	Yes=1	No=0	
Item 8 physical tiredness	Yes=1	No=0	
Item 9 problems with memory	Yes=1	Sometimes=0	No=0
Item 10 feeling down	Yes=1	Sometimes=1	No=0
Item 11 feeling nervous or anxious	Yes=1	Sometimes=1	No=0
Item 12 cope with problems	Yes=0	No=1	
Item 13 living alone	Yes=1	No=0	
Item 14 lack of social relations	Yes=1	Sometimes=1	No=0
Item 15 social support	Yes=0	No=1	

Supplementary Table S2 Versions of The Tilburg Frailty Indicator (TFI)utilized in five countries

Country	Versions of TFI
Spain	**A1** **¿Se siente físicamente sano?** ☐ Si ☐ No **A2** **¿Ha perdido mucho peso recientemente de forma involuntaria?** (6 kg o más en los últimos *6 meses* o 3kg o más en el *último mes*) ☐ Si ☐ No **¿Ha experimentado problemas en su vida diaria como:** Si / No **A3** ... dificultad para caminar? ☐ ☐ **A4** ... dificultad para mantener el equilibrio? ☐ ☐ **A5** ... peor audición? ☐ ☐ **A6** ... peor visión? ☐ ☐ **A7** ... pérdida de fuerza en las manos? ☐ ☐ **A8** ... cansancio? ☐ ☐ **Componentes psicológicos:** Si / Alguna vez / No **A9** ¿Ha tenido problemas de memoria? ☐ ☐ ☐ **A10** ¿Se ha sentido triste en el último mes? ☐ ☐ ☐ **A11** ¿Se ha sentido nervioso o con ansiedad? ☐ ☐ ☐ **A12** ¿Es capaz de enfrentarse a los problemas? ☐ ☐ **Componentes sociales:** Si / Alguna vez / No **A13** ¿Vive solo? ☐ ☐ **A14** ¿A veces echa de menos tener gente alrededor? ☐ ☐ ☐ **A15** ¿Recibe suficiente ayuda de otras personas? ☐ ☐

Greece

A1 **Αισθάνεστε σωματικά υγιής;**

☐ Ναι ☐ Όχι

A2 **Έχετε χάσει πρόσφατα πολύ βάρος χωρίς να το επιδιώξατε;**
(«πολύ» είναι: 6 κιλά ή παραπάνω κατά τους τελευταίους έξι μήνες ή 3 κιλά ή παραπάνω κατά τον τελευταίο μήνα);

☐ Ναι ☐ Όχι

Αντιμετωπίζετε προβλήματα στην καθημερινή σας ζωή λόγω:	Ναι	Όχι
A3 ... δυσκολίας στο περπάτημα;	☐	☐
A4 ... δυσκολίας στη διατήρηση της ισορροπίας σας;	☐	☐
A5 ... κακής ακοής;	☐	☐
A6 ... κακής όρασης;	☐	☐
A7 ... αδυναμίας στα χέρια σας;	☐	☐
A8 ... σωματικής κούρασης;	☐	☐

Ψυχολογικές συνιστώσες:	Ναι	Μερικές φορές	Όχι
A9 Έχετε προβλήματα με τη μνήμη σας;	☐	☐	☐
A10 Αισθανθήκατε πεσμένος/η ψυχολογικά τον τελευταίο μήνα;	☐	☐	☐
A11 Αισθανθήκατε εκνευρισμό ή άγχος τον τελευταίο μήνα;	☐	☐	☐
A12 Αντιμετωπίζετε καλά τα προβλήματά σας;	☐		☐

Κοινωνικές συνιστώσες:	Ναι	Μερικές φορές	Όχι
A13 Ζείτε μόνος/η;	☐		☐
A14 Σας λείπει καμιά φορά η παρουσία άλλων ανθρώπων γύρω σας;	☐	☐	☐
A15 Λαμβάνετε αρκετή υποστήριξη από άλλους ανθρώπους;	☐		☐

Croatia

A1 **Osjećate li se fizički zdravi?**

☐ Da ☐ Ne

A2 **Da li ste nedavno izgubili mnogo na težini bez da ste to željeli?**
("mnogo" znači: 6kg ili više u posljednjih 6 mjeseci ili 3kg i više u posljednjih mjesec dana)

☐ Da ☐ Ne

Osjećate li probleme u svakodnevnom životu koji su posljedica:	Da	Ne
A3 ... otežanog hodanja?	☐	☐
A4 ... problema s ravnotežom?	☐	☐
A5 ... oslabljenog sluha?	☐	☐
A6 ... oslabljenog vida?	☐	☐
A7 ... nedostatka snage u rukama?	☐	☐
A8 ... izičkog umora?	☐	☐

Psihološka dimenzija:	Da	Ponekad	Ne
A9 Imate li poteškoća s pamćenjem?	☐	☐	☐
A10 Jeste li se osjećali potišteno u zadnjih mjesec dana?	☐	☐	☐
A11 Jeste li se osjećali nervozno ili tjeskobno u zadnjih mjesec dana?	☐	☐	☐
A12 Možete li se dobro nositi s problemima?	☐		☐

Društvena dimenzija:	Da	Ponekad	Ne
A13 Živite li sami?	☐		☐
A14 Nedostaju li Vam ponekad ljudi u Vašoj okolini?	☐	☐	☐
A15 Primate li dovoljnu potporu od ljudi iz Vaše okoline?	☐		☐

the Netherlands

A1 **Voelt u zich lichamelijk gezond?**
☐ Ja ☐ Nee

A2 **Bent u de afgelopen periode veel afgevallen zonder dit zelf te willen?**
(Veel is: 6 kg of meer in de afgelopen 6 maanden of 3 kg of meer in de afgelopen maand)
☐ Ja ☐ Nee

Heeft u problemen in het dagelijks leven door ...	Ja	Nee
A3 ... slecht lopen?	☐	☐
A4 ... het slecht kunnen bewaren van uw evenwicht?	☐	☐
A5 ... slecht horen?	☐	☐
A6 ... slecht zien?	☐	☐
A7 ... weinig kracht in uw handen?	☐	☐
A8 ... lichamelijke moeheid?	☐	☐

Psychische componenten	Ja	Soms	Nee
A9 Heeft u klachten over uw geheugen?	☐	☐	☐
A10 Heeft u zich de afgelopen maand somber gevoeld?	☐	☐	☐
A11 Heeft u zich de afgelopen maand nerveus of angstig gevoeld?	☐	☐	☐
A12 Kunt u goed omgaan met problemen?	☐		☐

Sociale componenten	Ja	Soms	Nee
A13 Woont u alleen?	☐		☐
A14 Mist u wel eens mensen om u heen?	☐	☐	☐
A15 Ontvangt u voldoende steun van andere mensen?	☐		☐

the United Kingdom

A1 **Do you feel physically healthy?**
☐ Yes ☐ No

A2 **Have you lost a lot of weight recently without wishing to do so?**
('a lot' is: 6 kg or 13lbs or more during the last *six months*, or 3kg or 6½lbs or more during *the last month*)
☐ Yes ☐ No

Do you experience problems in your daily life due to:	Yes	No
A3 ... difficulty in walking?	☐	☐
A4 ... difficulty maintaining your balance?	☐	☐
A5 ... poor hearing?	☐	☐
A6 ... poor vision?	☐	☐
A7 ... lack of strength in your hands?	☐	☐
A8 ... physical tiredness?	☐	☐

Psychological components	Yes	Some-times	No
A9 Do you have problems with your memory?	☐	☐	☐
A10 Have you felt down during the last month?	☐	☐	☐
A11 Have you felt nervous or anxious during the last month?	☐	☐	☐
A12 Are you able to cope with problems well?	☐		☐

Social components	Yes	Some-times	No
A13 Do you live alone?	☐		☐
A14 Do you sometimes miss having people around you?	☐	☐	☐
A15 Do you receive enough support from other people?	☐		☐

5

Chapter 5

A coordinated preventive care approach for healthy ageing in five European cities: A mixed methods study of process evaluation components

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ABSTRACT

Aims To evaluate specific process components of the Urban Health Centres Europe (UHCE) approach; a coordinated preventive care approach aimed at healthy ageing by decreasing falls, polypharmacy, loneliness and frailty among older persons in community settings of five cities in the United Kingdom, Greece, Croatia, the Netherlands and Spain.

Design Mixed-methods evaluation of specific process components of the UHCE approach: reach of the target population, dose of the intervention actually delivered and received by participants and satisfaction and experience of main stakeholders involved in the approach.

Methods The UHCE approach intervention consisted of a preventive assessment, shared-decision making on a care plan and enrolment in one or more of four coordinated care-pathways that targeted falls, polypharmacy, loneliness and frailty. Quantitative data from a questionnaire and quantitative/qualitative data from logbooks were collected among older persons involved in the approach. Qualitative data from focus-groups were collected among older persons, informal caregivers and professionals involved in the approach. Quantitative data were analysed by means of descriptive statistics and multilevel logistic regression models. Qualitative data were analysed through thematic analysis.

Results Having limited function was associated with non-enrolment in falls and loneliness care-pathways (both $P < 0.01$). The mean rating of the approach was 8.3/10 (SD = 1.9). Feeling supported by a care professional and meeting people were main benefits for older persons. Mistrust towards unfamiliar care providers, lack of confidence to engage in care activities and health constraints were main barriers towards engagement in care.

Conclusions Although the UHCE approach was received generally positively, health constraints and psychosocial barriers prevented older person's engagement in care.

Impact Coordinated preventive care approaches for older community-dwelling persons should address health constraints and psychosocial barriers that hinder older person's engagement in care.

KEYWORDS Coordinated care; Frailty; Mixed methods study; Nurses; Older persons; Prevention; Primary care; Process evaluation

INTRODUCTON

Europe has the highest proportion of persons over 65 years compared to any other continent.[1] As the number of older persons is increasing, there will be relatively fewer beds available in inpatient care facilities. Because of this, it is important to have a well-functioning primary care system that promotes healthy ageing among older persons. The European Union has identified priority areas for healthy ageing, which are: polypharmacy, falls and frailty.[2] These are highly prevalent among older persons, and are associated with negative health outcomes and higher care use.[3-5] Loneliness is another large problem among older persons; around 20-30% report loneliness[6]. Loneliness has been associated with frailty[7] and a fall in the previous year[8]. Hence, the co-occurrence of these and other health problems is common.[9, 10]

Coordinated preventive care interventions which integrate health and social care services have been proposed to address health problems among older persons.[11, 12] These interventions usually include a preventive multidimensional assessment of health, development of a care plan and coordinated care.[13-15] This care plan is often made through a process of shared decision-making, in which the patient is involved in care decisions.[16] Care coordination is typically done by a nurse to alleviate the workload for the general practitioner.

Background

Evidence for a positive effect of coordinated preventive care interventions on quality of life and independent functioning among older persons is mixed.[17-20] This may be explained by differences in groups reached by the intervention, fidelity to the intervention and context of implementation. However, a recent study revealed that coordinated preventive care studies often do not report how such specific aspects of the intervention are carried out.[21] Insight in these so-called 'process components' could increase the understanding of underlying reasons for why some studies do find positive effects while another do not. Steckler and Linnan have developed a framework to study process components for public health interventions.[22, 23] In this framework, process components which are evaluated include: reach of the target population, dose of the intervention actually delivered to and received by participants, and satisfaction of main stakeholders with the intervention.22 The Stecklar and Linnan framework is recommended for the development and reporting of complex interventions.[24]

The Urban Health Centres Europe approach (UHCE approach) was a preventive coordinated care approach aimed at promoting healthy ageing by decreasing falls, polypharmacy, loneliness and frailty among community-dwelling older persons.[25] The UHCE approach consisted of a preventive assessment of fall risk, polypharmacy, loneliness and frailty and, only if the person had a need or indication for care, shared-decision making on a care plan and enrolment in coordinated care-pathways.[26] The UHCE approach showed promising, but minor positive effects in tackling recurrent falls and frailty and promoting physical health-related quality of life and mental well-being compared to care as usual.[26] Further, only 54%

of older persons enrolled in care-pathways. As part of the UHCE study, process components of the implementation of the UHCE approach were evaluated as proposed by Steckler and Linnan. By evaluating these process components, we want to improve the understanding of the reasons for the low enrolment and minor effects found in the UHCE approach. The current evaluation could also aid the future development and implementation of similar interventions.

THE STUDY

Aims

The aim of this study is to evaluate specific process components of the UHCE approach among older persons in community settings of five European cities. The following research questions are answered:

1) What population was reached by the UHCE approach?
2) What dose of the intervention was actually delivered and received and by which participants?
3) What was the satisfaction and experience of main stakeholders involved in the UHCE approach?

Intervention

The development of the UHCE approach intervention has been previously described.[25, 26] A general template for the UHCE approach was developed based on systematic literature searches of evidence-based interventions and focus group discussions with main stakeholders. The general UHCE template consisted of three stages (Figure 1).

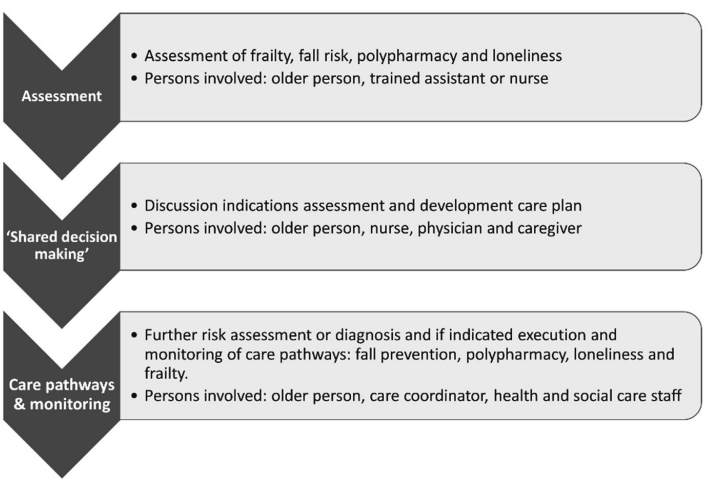

Figure 1 The Urban Health Centres Europe approach (from Franse et al. 2017)

The first stage involved a preventive health assessment at the older person's home or at a health centre. This was done in order to identify if there was a need or indication for follow-up care-pathway(s). For this purpose, a short uniform assessment form was developed, which was to be used in all cities. The assessment consisted of instruments that had been previously validated. These instruments assessed 1) risk of falling; based on a protocol by Dutch safety research institute[27], 2) polypharmacy; based on using five or more different medicines[28] and/or difficulty in taking medications as prescribed, 3) loneliness; based on Jong-Gierveld loneliness scale[29], and 4) frailty; based on the Tilburg Frailty Indicator[30]. The assessment was piloted in at least five older persons in each city. For the questions that were not interpreted correctly, minor changes were made.

The second stage of the UHCE approach consisted of shared-decision making. When the results of the assessment indicated a need for follow-up care, a care plan was to be developed together with the older person, this was done to promote his/her involvement in care-pathways. The UHCE template recommended discussing the results of the assessment at least between the older person, the person in charge of care coordination and the physician. Because informal caregivers can have an important role in the older person's care, care teams were encouraged to ask the older person to involve an informal caregiver such as a partner or relative in shared-decision making.

The third stage of the UHCE approach consisted of referral to care-pathways. After a shared-decision on an individualized care plan was made, each participant was to be referred to care-pathways according to their indication and preferences. The main care-pathways were: 1) fall prevention actions, 2) actions addressing polypharmacy (adherence and/or appropriate prescribing actions), 3) actions addressing loneliness, and 4) frailty and other medical actions; frailty actions and other medical care which the healthcare provider deemed necessary and which did not fall under care-pathways 1-3 was given in this care-pathway. The general template of the UHCE approach included evidence-based interventions for each care-pathway based on systematic literature searches, which were to be used by the cities. The care coordinator was asked to monitor the progress of each individual care plan under the supervision of a physician.[26]

Ethical considerations

Ethical committee procedures were followed in all cities, and approval was provided. Written consent was obtained from all participants. The study was registered in the ISRCTN registry under number ISRCTN52788952.

Context & implementation

The general template of the UHCE approach was subsequently implemented in the context of primary care and community settings in five European cities (Greater Manchester, United Kingdom; Pallini, Greece; Rijeka, Croatia; Rotterdam, the Netherlands; and Valencia, Spain). The place of assessment, type of care-pathways, staff involved and context of each of the five participating cities are described in more detail in Table 1.

Table 1 Context of the cities involved in UHCE

	Manchester, UK	Pallini, GR	Rijeka, HR	Rotterdam, NL	Valencia, ES
Location UHCE approach	General practices in Tameside and Glossop districts	Municipality/senior centres Pallini	General practices in Western Rijeka	Primary health center in Ommoord neighbourhood	Primary health center in Nou Moles neighbourhood
Assessment	At home by trained assistant	At senior/health centre by health professional	At home by community nurse	At home by trained assistant	At home by trained assistant
Care coordinator	Trained assistant supervised by GP	Health professional or social worker	Community nurse	Geriatric nurse practitioner	Trained assistant supervised by GP
Type of care in care-pathways	Multiple per pathway; e.g. home adjustment by OT, walking group by volunteers (falls); medication review by GP (polypharmacy); buddying services by volunteers (loneliness); further care by GP (frailty).	Group based endurance and balance training by PE (falls); self-managed medication adherence App supported by physician (polypharmacy); support groups by psychologist (loneliness); further care by physician (frailty).	Group based balance and strength training by PT (falls and frailty); self-managed medication adherence App (polypharmacy); social group activities (loneliness).	Multiple per pathway; e.g. physiotherapy by PT (falls); medication review by pharmacist (polypharmacy); social activities (loneliness); further care by GP (frailty).	Group based balance and strength training by PT (falls and frailty), medication review according to national protocol by GP (polypharmacy), social support group led by social worker (loneliness).
Care existing or newly developed	All existing; offered by local charity organisation and according to practice GP	All newly developed	Falls, frailty and polypharmacy newly developed. Loneliness existing services	All existing, medical care according to practice GP and social care by local organizations	Falls, frailty and loneliness newly developed. Polypharmacy existing protocol

Abbreviations: ES, Spain; GP, general practitioner; GR, Greece; HR, Croatia; NL, The Netherlands; OT, occupational therapist; PE, physical educator; PT, physical therapist; UK, United Kingdom.

In all cities, except for Pallini, general practices were involved in the UHCE approach. In Pallini, the UHCE approach was provided by a health team from the municipal health centre newly employed for this study. The health assessment took place at the person's home in all cities except for Pallini, where the assessment took place at a community centre. In Rotterdam and Manchester, the UHCE approach made use of existing care interventions. In Rijeka and

Valencia, some new care provisions were newly developed and in Pallini all care provisions were newly developed.

Falls care-pathways varied among settings, including group-based exercise programs, home adjustments and physiotherapy. In Rijeka and Valencia persons who had a frailty indication were offered to enrol in the falls care-pathway. In Rijeka and Pallini, the polypharmacy care-pathway included a self-managed medication adherence application. In the other settings, persons entering this care-pathway received a medication review by a pharmacist. The loneliness care-pathway included group-based activities and support groups. No additional monetary incentives were provided to staff within existing care. In settings where new care provisions were developed, the staff was hired on a voluntary bases or sometimes compensated. The participants received no monetary incentives. For some of the interventions, participants borrowed materials that were needed for care activities.

Design

We applied a convergent mixed-methods evaluation design[31] alongside the effect evaluation of the UHCE approach. This was done in all cities between May 2015 and June 2017. Quantitative and qualitative data was collected and analysed separately.

Participants

Older persons and informal caregivers

The target population consisted of persons living independently, aged 75 years or older, who were, according to their physician, able to participate in a care-pathway for at least 6 months. This timeline was chosen because the care pathways were to last at least 6 months. In two cities; Pallini and Valencia, the age of the population was lowered to 70 years or older due to difficulties encountered during recruitment. Older persons who participated were recommended to involve an informal caregiver, particularly in shared-decision making, as described earlier. Older persons were not eligible to participate if they were not able to comprehend information in the local language or if they were unable to cognitively evaluate the risks/benefits of participation and were not expected to make an informed decision regarding participation, according to their physician.[25] We aimed for a purposeful sample of 250 older persons in each city, as previously described.[25]

Professionals

In each city, health and social care professionals participated in the UHCE approach. Care decisions were made by a physician, together with a care coordinator, older person and sometimes an informal caregiver. Other professionals involved in the care-pathways were physiotherapists, occupational therapists, physical educators, psychologists, social workers, pharmacists and volunteers, depending on context as described in Table 1.

Data collection

Specific process components were evaluated: reach of the target population, dose of the intervention actually delivered and received by participants, and satisfaction and experience of main stakeholders with the intervention as proposed by Stecklar and Linnan.[22] Table 2

presents an overview of process evaluation components for each study question and the way these were measured in the study.

Questionnaire

A quantitative questionnaire was developed mainly for the purpose of the effect evaluation of the UHCE approach. It was administered to older persons at baseline and at follow-up after 12 months. To study reach and dose received; characteristics of participants who were lost to follow-up and characteristics of participants who did not enrol in care-pathways (Table 2; question 1.2 and 2.2), we used 10 items included in the baseline questionnaire: age (in years), sex (male/female), living situation (alone/not alone), education level (low/high; based on International Standard Classification of Education; ISCED)[32], function (limited/not limited; based on Global Activity Limitation Index; GALI)[33, 34] and mental health (poor/good; based on 5-item mental well-being scale of the SF-36)[35].

To study satisfaction with the UHCE approach (Table 2; question 3.1), we used 5 items included in the follow-up questionnaire. Four items measured whether persons agreed on being satisfied with each of the three UHCE stages on a five point Likert scale. Answers were categorized into 'agree/strongly agree' and 'neither agree nor disagree/disagree/strongly disagree'. A final item rated person's satisfaction with the UHCE approach on a scale from 1 to 10.

Items that were not available in local language (age, sex, living situation and satisfaction with the UHCE approach) were developed in English and translated into local languages. Items were translated into the local languages and backward into English. Backward English translations were discussed among the study team and translation was adapted when needed. In each city, the questionnaire was piloted in at least five older persons. When questions were misinterpreted by participants, minor changes were made.

Logbooks

To study dose delivered to and received by the participants (Table 2; question 2.1 and 2.3), a logbook was developed for all cities. This logbook was kept for each older person involved in the UHCE approach. In this logbook, quantitative information of the delivery and involvement of the older person in the three stages of the UHCE approach was kept: 1) Whether or not a health assessment took place and whether the participant had an indication for any care-pathways, 2) Whether or not shared decision making took place, and 3) Whether or not the participant followed any care-pathways. Additionally, an open-ended qualitative question on the reason for not enrolling into any care-pathways was included. After 6 months at least, the care coordinator documented (if needed contact was made with either the participant or responsible health care provider) whether the three stages of the UHCE approach were delivered. The paper logbooks were subsequently entered into an electronic data-entry form. Electronic data were checked for missing/incorrect data.

Table 2 Components of the process evaluation, related research questions and method of measurement

Component	Research question	Measurement			
		Log books	Focus groups	Questionnaire	Project register
Reach	**1. What population was reached by UHCE approach?**				
	1.1 How many persons accepted to participate in the UHCE approach?				X
	1.2 What were characteristics of persons who were lost to follow-up between baseline and follow-up?			X	
Dose delivered and received	**2. What dose of the intervention was actually delivered and received by which participants?**				
	2.1 To what extent were three stages of the UHCE approach (assessment, shared-decision making, care-pathways) delivered to older persons?	X			
	2.2 What were characteristics of persons who did not enroll in care-pathways?			X	
	2.3 What were reasons for non-enrolment in care-pathways?	X			
Satisfaction and experience	**3. What was the satisfaction and experience of main stakeholders involved in the UHCE approach?**				
	3.1 Were older persons satisfied with the UHCE approach?			X	
	3.2 What benefits, barriers and improvements did older persons, informal caregivers and professionals report?		X		

Abbreviations: UHCE, Urban Health Centres Europe

Focus groups

To study the experience of main stakeholders involved (Table 2; question 3.2), focus groups[36] of 40 minutes to 1 hour each were held around the time of the follow-up assessment 12 months after baseline with older persons, informal caregivers and professionals. Semi-structured topic guides (Supplementary Table S1) were developed which included the following topics: 1) overall experience with the UHCE approach, 2) experience with the health assessment and care-pathways, and 3) experience with shared-decision making. For each of these topics, the guide included probe questions about benefits, barriers and improvements participants identified. In Manchester, two focus groups with five older persons/informal caregivers each were organized, in all other cities one focus group with 5 older persons/informal caregivers was organized. Older persons and caregivers with the following criteria were selected: being physically and mentally able to participate in the focus group and enrolled (or the person they cared for enrolled) in at least one care-pathway. In each city except Manchester, one focus group with four to six social and health care professionals was

organized. This number allowed us to select professionals with varied professions who had been actively involved in the UHCE approach. In Manchester, two actively involved trained assistants were interviewed. In total: 26 older persons, four informal caregivers and 22 professionals were included (7 nurses, 4 general practitioners/physicians, 2 physical/occupational therapists, 2 social workers, 2 trained assistants, 1 physical education teacher, 1 pharmacist, 1 volunteer, 1 care manager, 1 municipality officer). Supplementary Table S2 described the numbers by city. The focus group discussions and in-depth interview were recorded, transcribed into the local language and translated into English if applicable.

Data analysis

Quantitative data were summarised using descriptive statistics (frequencies, means and percentages). Characteristics of persons included at follow-up and persons who dropped out were compared by means of chi-square tests for categorical variables and one-way ANOVA for continuous variables. We further compared characteristics of persons who enrolled in a specific care-pathway (falls, polypharmacy, loneliness and frailty) with persons who did not enrol in that care-pathway but had an indication to receive that care-pathway. For this purpose, multilevel random-intercept logistic regression was used because data was clustered by city.[37] We built 4 separate models for each care-pathway in which we analysed the association of independent variables age, sex, living situation, education level, function and mental health with dependent variable non-enrolment. We corrected the effect estimates for all factors as well as clustering effects by city. We considered a P-value of 0.05 or lower to be statistically significant. All quantitative analyses were performed using SPSS version 23.0 (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp).

For the qualitative data from the focus groups and logbooks, the thematic analysis method was used.[38] Focus group transcripts were read multiple times by CF and XZ and meaningful overarching themes and subthemes were identified and summarized in a coding table. The coding table was discussed among the authors and refined. Subsequently, applicable quotes from the transcripts were entered into the coding table and categorized according to subtheme. Overarching themes confirmed topics in the topic guide that was used for the focus groups: benefits/barriers of the health assessment, benefits/barriers of the care-pathways, and recommendations for improvement. Meaningful subthemes emerged from the raw data (e.g. under the overarching theme ‘barriers of the care-pathways’, subthemes ‘mistrust’ and ‘embarrassment’ emerged). Qualitative logbook data on the older person’s reason(s) for not enrolling into any care-pathways were coded into meaningful themes in an excel sheet by CF. Subsequently, XZ coded the data into the themes developed by CF. Coding by the two authors was compared and disagreements in coding were discussed and resolved. If necessary, themes were refined by discussion between authors.

Rigour

The design of this study was based on a theoretical framework for process evaluations of public health interventions developed by Stecklar and Linnan.[22] Using an established theoretical framework in the development and reporting of complex interventions improves

transparency.[24] We used a combination of quantitative and qualitative methods to study process components. This has the benefit of being able to confirm findings with different methods, thus increasing validity.[39] The qualitative data analysis was performed independently by two researchers and compared to increase the reliability of the coding of qualitative information.[38]

RESULTS

Reach

Overall, 2,825 persons were invited to participate in the UHCE approach and 1,215 persons (43.0%) accepted the invitation and completed the baseline health assessment (Table 3). Of these persons, 986 persons (81.2%) completed the follow-up questionnaire at 12-month follow-up. A comparison of persons included at follow-up (N = 986) with persons who dropped out of the study after baseline (N = 229) did not indicate significant differences in terms of sex (P = 0.164), living situation (*P* = 0.519), function (*P* = 0.593) and mental health (*P* = 0.463), but these persons were older (*P* < 0.001) and lower educated (*P* = 0.001).

Dose delivered and received

Of the 986 persons who received the UHCE approach, according to the UHCE template; 80.5% had an indication; 50.9% had a fall risk indication, 50.2% had a polypharmacy indication, 28.4% had a loneliness indication and 54.0% had a frailty indication (Table 3). Indications for care-pathways, as reported in logbooks differed from those proposed in the UHCE template; 85.6% had an indication. Having an indication as reported in logbooks varied between 74.1% in Manchester to 100% in Rijeka. Shared-decision making was done with almost all participants. In total, 520 persons (53.6%) enrolled in any of the care-pathways. Enrolment in any care-pathway varied between 99.5% in Rijeka to 14.6% in Rotterdam. Across all cities; 28.6% enrolled in the falls care-pathway, 23.0% enrolled in the loneliness care-pathway, 13.7% enrolled in the polypharmacy care-pathway and 9.9% enrolled in the frailty/medical care-pathway.

Characteristics associated with non-enrolment in care-pathways among older persons involved in the UHCE approach are presented in Table 4. Limited function was positively associated with non-enrolment in the falls and loneliness care-pathways (*P* < 0.01). Female gender was positively associated with non-enrolment in the polypharmacy care-pathway, but negatively associated with non-enrollment in the loneliness care-pathway (*P* < 0.05).

The reasons older persons reported for why they did not enroll in care-pathways are presented in Table 5. Of the 466 persons who were non-enrolled, 326 (70.0%) did have an indication for a care-pathway according to the logbooks. Of those, 173 persons reported a reason for non-enrolment; 91 from Manchester, 45 from Rotterdam, 29 from Pallini and 8 from Valencia. Most persons (28.3%) reported that they wanted to deal with health problem themselves, many also reported already being involved in other care or exercise (22.0%). All

but one person who reported these reasons were from Manchester or Rotterdam. In all cities, persons reported that health problems preventing participation (11.6%).

Table 3 Reach and dose delivered for each stage of the UHCE approach

Stage	Total N (%)	Manchester N (%)	Pallini N (%)	Rijeka N (%)	Rotterdam N (%)	Valencia N (%)
Invited for UHCE approach	2825	1166	500	277	512	370
Completed baseline health assessment	1215(40.3)	274(23.5)	190(38.0)	249(89.9)	243(47.5)	259(70.0)
Completed follow-up questionnaire	986(81.2)	212(77.4)	154(81.1)	221(88.8)	192(79.0)	207(79.9)
Any indication as in UHCE template[a]	794(80.5)	173(81.6)	132(85.7)	190(86.0)	147(76.6)	152(73.4)
Fall risk indication	502(50.9)	114(53.8)	69(44.8)	129(58.4)	85(44.3)	105(50.7)
Polypharmacy indication	495(50.2)	132(62.3)	83(53.9)	100(45.2)	104(54.2)	76(36.7)
Loneliness indication	280(28.6)	26(12.4)	62(40.5)	102(46.6)	46(24.1)	44(21.3)
Frailty/medical indication	532(54.0)	100(47.2)	105(68.2)	140(63.6)	81(42.2)	106(51.2)
Any indication reported as in logbooks[a]	831 (85.6)	157(74.1)	144(93.5)	220(100)	145(81.5)	165(79.7)
Fall risk indication	549(56.5)	114(53.8)	74(48.1)	168(76.4)	75(42.1)	118(57.0)
Polypharmacy indication	322(33.9)	9(0.04)	49(31.8)	116(52.7)	88(49.4)	60(32.1)
Loneliness indication	464(47.8)	89(42.0)	109(70.8)	153(69.5)	46(25.8)	58(31.0)
Frailty/medical indication	314(33.0)	101(47.6)	71(46.1)	165(74.7)	83(46.6)	67(32.4)
Shared decision making[a]	969(98.3)	212(100)	154(100)	220(99.5)	176(91.7)	207(100)
Enrollment any care-pathway[a]	520(52.7)	47(22.2)	112(72.7)	220(99.5)	28(14.6)	113(54.6)
Enrollment Falls care-pathway	278(28.6)	39(18.4)	24(15.6)	143(65.0)	0[b]	72(34.8)
Enrollment Polypharmacy care-pathway	130(13.7)	2(0.9)	46(29.9)	22(10.0)	5(2.8)[b]	55(29.4)
Enrollment Loneliness care-pathway	223(23.0)	4(1.9)	55(35.7)	133(60.5)	1(0.6)[b]	30(14.5)
Enrollment Frailty/medical care-pathway	94(9.9)	16(7.5)	53(34.4)	NA	25(14.0)	NA

Note: Missing items: Indication for care-pathway as in UHCE template; Frailty =1, Loneliness =7; Indication for care-pathway as reported in logbooks; Frailty=35, Falls=15, Polypharmacy=35, Loneliness=15; Enrollment in any care-pathway=4; Frailty=24, Falls=4, Polypharmacy=24, Loneliness=4.
Abbreviations: NA, not applicable; UHCE, Urban Health Centres Europe.

[a] The percentage reported is of the participants who completed the follow-up questionnaire and with complete information for the item.

[b] These are persons finishing the care-pathway; respectively 23, 90 and 7 persons followed the falls, polypharmacy and loneliness care-pathways without formally finishing it.

Table 4 Multilevel logistic regression on factors associated with non-enrolment among persons enrolled in the care-pathway and persons not enrolled in the care-pathway who had an indication for the care-pathway.

	Falls care-pathway			Polypharmacy care-pathway			Loneliness care-pathway			Frailty/medical care-pathway		
	Enrolled N=278	Not Enrolled N=283	OR (95% CI)[a]	Enrolled N=130	Not Enrolled N=355	OR (95% CI)[a]	Enrolled N=223	Not Enrolled N=167	OR (95% CI)[a]	Enrolled N=94	Not Enrolled N=857	OR (95% CI)[a]
Age ≥80 years	132 (47.5)	305 (44.0)	1.38 (0.87, 2.19)	51 (39.2)	381 (46.4)	0.59 (0.32, 1.10)	101 (45.3)	336(44.9)	0.97 (0.57, 1.65)	41 (43.6)	391 (45.6)	0.96 (0.52, 1.76)
Female	195 (70.1)	181 (64.0)	0.77 (0.48, 1.23)	66 (50.8)	207 (58.3)	**2.30 (1.25, 4.24)****	159 (71.3)	109 (65.3)	**0.50 (0.28, 0.89)***	59 (62.8)	514 (60.0)	1.00 (0.56, 1.80)
Low education	152 (54.7)	153 (54.3)	0.68 (0.42, 1.10)	89 (68.5)	157 (44.4)	0.64 (0.35, 1.17)	110 (49.3)	98 (58.7)	1.73 (0.98, 3.03)	55 (59.1)	425 (49.7)	0.83 (0.47, 1.44)
Living alone	105 (37.8)	136 (48.1)	0.93 (0.58, 1.49)	38 (29.2)	153 (43.1)	0.71 (0.37, 1.36)	84 (37.7)	87 (52.1)	1.17 (0.68, 2.02)	34 (36.2)	331 (38.6)	1.78 (0.98, 3.23)
Limited function	164 (59.2)	199 (70.3)	**1.92 (1.22, 3.03)****	85 (65.4)	236 (66.9)	0.75 (0.41, 1.37)	124 (55.9)	125 (75.3)	**2.10 (1.23, 3.43)****	68 (73.1)	435 (50.9)	0.84 (0.46, 1.53)
Poor mental health	47 (17.0)	40 (14.2)	1.42 (0.80, 2.53)	24 (18.8)	42 (11.8)	1.56 (0.76, 3.21)	53 (23.9)	38 (22.9)	1.05 (0.60, 1.86)	14 (15.1)	94 (11.0)	0.99 (0.45, 2.18)

Note: Missing items: falls care-pathway; low education=1, limited foundation=1, poor mental health=2; polypharmacy care-pathway; low education=1, limited foundation=2, poor mental health=2; loneliness care-pathway; limited foundation=2, poor mental health=2; frailty/medical care-pathway; low education=3, limited foundation=3, poor mental health=4

[a] Values are derived from random-intercept multilevel logistic regression models adjusted for clustering by city and adjusted for age, gender, education, living situation, function and mental health.

Values in bold are statistically significant: *p-value < .05, **p-value < .01.

Table 5 Reasons participants reported why they did not enroll in care-pathways (N=173)

Reason reported[a]	N (%)
Wants to deal with it themselves	49 (28.3)
Does not want	47 (27.2)
Involved other care or exercise	38 (22.0)
Health problems prevent participation	20 (11.6)
Interested but not yet applied	15 (8.7)
Feels too healthy	9 (5.2)
Too far/transportation difficulties	9 (5.2)
Too busy to participate	6 (3.5)
Moved	2 (1.2)
Care for someone, too busy	2 (1.2)

[a] Multiple reasons could be reported per person

Satisfaction and experience

Satisfaction with the UHCE approach among older persons is reported in Table 6. Persons were generally satisfied with the UHCE approach. Overall, 82.1% of persons in all cities felt they had benefitted from the health assessment and 85.4% of persons felt it was worth the time and effort. The mean rating of the UHCE approach was 8.3 (SD = 1.9) out of 10, ranging from 6.5 (SD = 2.4) in Pallini to 9.3 (SD = 1.2) in Manchester.

In the focus groups, several benefits of the UHCE approach for older persons and care professionals were identified. A benefit according to older persons and professionals, which was identified in all cities, was that older persons valued the feeling that someone looked out for them; either the care coordinator or care professionals in the care-pathways. Another benefit according to older persons and professionals in most cities was that older persons valued meeting other people. The group-based care-pathways of UHCE had given older persons involved in these activities the opportunity to meet others. An older woman in Valencia commented on the social support group: “I liked it a lot, it helped me to open up to people”. A benefit according to older persons and professionals in several cities was that results from the assessment and contact with care professionals had motivated older persons to take action regarding their health. Several benefits for care professionals were identified in the focus group with care professionals in Rotterdam. A key benefit was that using a structured preventive assessment for recording older person’s health had aided in future care decisions, because care professionals were able to look back in the records.

Some barriers and recommendations were also identified. One of the main barriers for older person’s engagement in care according to care professionals in all cities was mistrust among older persons towards unfamiliar care professionals and activities. A recommendation made by care professionals in several cities which related to this was the importance of building a trusted relationship with clients. A geriatric nurse in Rotterdam said: “You have to invest in it [the relationship], once the trust is there then the older person will follow your advice”. Another main barrier according to older persons in most cities was feeling embarrassed or

lacking confidence about engaging in activities. An older woman in Valencia said: "I think I told you of my fall, but since then I have just lost complete confidence in going anywhere". An older man in Manchester explained: "There were clubs to join but I just didn't have the confidence, when you live on your own you get introverted". A barrier which was identified by both older persons and health professionals in all cities were health constraints of older persons. This also appeared to prevent engagement in care-pathways that required more activity or travel. A recommendation that was made by care professionals in Rijeka, was to further adapt preventive care activities to needs of specific groups of older persons such as persons with chronic illnesses. Specific barriers for care professionals in several cities were time constraints and unfamiliarity of health professionals in collaborating with social care professionals. Finally, the most common recommendation according to older persons and health professionals in Pallini, Rijeka and Valencia, where activities were not embedded in existing care, was to continue activities beyond the project.

Table 6 Satisfaction among older persons with the UHCE approach

Satisfaction statements	Total	Manchester	Pallini	Rijeka	Rotterdam	Valencia
Agree or strongly agree; n/N (%)						
I can benefit from the health assessment	630/767 (82.1)	167/212 (78.8)	76/104 (73.1)	194/221 (87.8)	13/23 (56.5)	180/207 (87.0)
The health assessment was worth the time and effort	650/761 (85.4)	189/211 (89.6)	74/99 (74.7)	192/221 (86.9)	15/23 (65.2)	180/207 (87.0)
I had a say in decisions about my health	372/474 (78.5)	2/3 (66.7)	65/97 (67.0)	199/221 (90.0)	16/23 (69.6)	90/130 (69.2)
I am satisfied with the care I received	433/532 (81.4)	5/5 (100)	75/111 (67.6)	191/221 (86.4)	15/23 (65.2)	146/171 (85.4)
Scale 1-10; mean±*SD*						
I am satisfied with the UHCE approach (scale 1-10)	8.3±1.9	9.3±1.2	6.5±2.4	8.3±1.8	7.9±0.9	8.8±1.5

Note: Missing/not applicable: Benefit from health assessment=219; Worth time and effort=225; Results discussed with me=622; Had a say in decisions=512; Satisfied with care=454; Satisfied UHCE approach=188.

DISCUSSION

In this study, we examined what dose of a coordinated preventive social and health care approach for older persons was delivered and received, which persons were reached and what their experience was with the approach. The UHCE approach was received generally positively. However, having limited function was associated with non-enrolment in specific care-pathways of the approach. Feeling supported by a care professional was mentioned as a benefit for older persons. Mistrust towards unfamiliar care providers and lack of confidence to engage in certain care activities were mentioned as barriers.

In a previous study we found minor effects of the UHCE approach on the lifestyle, health and quality of life of older persons and hypothesized that this was due to only around half of the

persons in the intervention group enrolling in care-pathways.[26] Quantitative and qualitative results from the current study imply that persons in poor health might have enrolled less often, especially in falls and loneliness care-pathways. Interventions in the falls and loneliness care-pathways required persons to move to the training location and included active activities such as balance and strength training or social group activities. Persons who were limited in function might have not been able to participate in these activities. In most cities, care in the other care-pathways for frailty and polypharmacy consisted of further assessment or referral to other care services. Which means these pathways required a less active involvement of older persons. Future interventions should develop strategies to reach older persons with limited functioning. Further adapting interventions to needs of groups with specific health problems were recommended by care professionals in this study. This is supported by findings from a large meta-analysis of complex care interventions which found no benefits of any specific type of intervention and recommended tailoring of interventions to client needs.[19] In Rotterdam and Manchester, where enrolment into care-pathways was particularly low, many persons reported wanting to solve health problems themselves and already being involved in other care as reasons for non-enrolment. As explained earlier[26], regular care for older persons in Manchester and Rotterdam was of high standard and the added benefit of the UHCE approach might have been small in these settings.[19]

Older persons were generally satisfied with the UHCE approach. A main benefit for older persons was feeling that a care professional looked out for them. Feeling supported by and experiencing a better relationship with the care provider has also been reported in other coordinated care interventions.[40-42] Trust appears to be the foundation of the relationship between care provider and older person and impacts on the acceptance of offered care.[43-45] Also in our study, mistrust among older persons towards unfamiliar services and care providers was a main barrier towards participation in care. Psychosocial reasons were also a barrier towards care uptake in our study. Some older persons did not want to engage in activities that could put them in awkward social situations. Others did not feel confident enough to travel to activity locations because they were afraid of falling. It is therefore important for care professionals to focus on these psychosocial factors that influence care decisions. Even more so, because older persons themselves appear to prefer that care professionals focus on their psychosocial context.[45]

There were differences between the health assessment indications as proposed in the general template and as used by cities. Cities reported sometimes using additional instruments or basing decisions on further clinical judgement. Cross-cultural adaptation of health assessment instruments could improve medical decision-making, such as has been done for the Tilburg Frailty Indicator in some countries.[46, 47] The extent of integration of the UHCE approach within the existing care system differed among cities. In Pallini, Rijeka and Valencia existing care was not available or referral to existing care was difficult. This could have impacted on the sustainability of the UHCE approach. Indeed, both participants and professionals in these cities mentioned they wished activities would continue beyond the project.

Strengths and limitations

The main strength of the current study is that we did an extensive evaluation of process components based on a theoretical framework proposed by Stecklar and Linnan.[22] By combining quantitative and qualitative methods we were able to deepen the understanding of the implementation of the UHCE approach. This study also has some limitations. First, logbooks were completed by staff involved in the UHCE approach. This might have caused a bias and positive reporting of the execution of logbook components. For example, cities reported that shared-decision making was done in almost 100% of cases. However, it was unclear how and to what extent the older person was involved in this process. Perhaps the definition of shared-decision making has been interpreted differently by cities. Secondly, older persons included in the focus groups might have been those that were most positive about the UHCE approach as these persons were selected by care professionals involved in the study. Third, there were many missings for the questions on satisfaction of the UHCE approach. Persons who did not answer could have thought these questions were not applicable to them because they were less involved in the UHCE approach. The responses could have therefore been biased towards the more active participants who might have been more positive about the UHCE approach. Further, although questions on satisfaction were translated from English to local languages and back-translated, there might have been cross-cultural differences in the interpretation of these questions. Last, we did not include a representative number of informal care-givers in the focus groups. Having the perspective of this group would have strengthened our findings.

CONCLUSIONS

Although coordinated prevented care appears to be received positively, there may be barriers that hinder person's engagement in care. Care activities that require transport or a higher level of activity might not reach older persons who are limited in their functioning and should be adapted for this group of older persons. Mistrust towards unfamiliar care providers and lack of confidence to engage in certain care activities are main barriers towards engagement in care among older persons. It is therefore important for care professionals to build a trusted relationship with their older clients and focus on psychosocial barriers that might affect their care decisions.

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Supplementary Table S1 Focus group: semi-structured topic guides

Focus group topic guide older persons & informal caregivers	
Introduction by the moderator:	
The past year you have been part of the research study Urban Health Centres Europe. This research project is a European project performed in five different countries, namely the United Kingdom, Spain, Greece, Croatia and the Netherlands. As part of this study you have received a home visit with a health assessment by a nurse or health care provider. With the results of this house-visit the care you receive might have been changed. This focus group interview is part of the evaluation of the UHCE study. We would like to know your opinion and experiences with this program the past year. This focus group will last about 40-60 minutes. The focus group interview will be audio-taped and the researcher will transcript this into a written transcript at a later date for the purpose of analysis. The information will be used anonymous, no names will be mentioned. With the information you give us our aim is to develop a template for an Urban Health Centre Europe that will be characterized by integrated health and social care for elderly living independently. My role as a moderator is only to facilitate in a lively and productive discussion. I am interested in your personal opinions, so please feel free to express yourself. Do you have any questions about this? Do you agree with participation in this focus group discussion and tape-recording of this focus group discussion? [If everyone agrees start audio-tape]	5 min
Introduction participants	
Please tell us a little bit more about yourself Probes: • What is your age? • Where and how do you live? • What care do you receive and from whom?	5 min
General experience with the UHCE assessment and care past year	
What was your overall opinion of the UHCE assessment and care program the past year? How is your health or well-being now compared to one year ago? Probes: • What were the major strengths of this care program? • What improvements can be made to this care program? • Would you recommend a friend of your age to enroll in the program? Why/why not?	15 min
Experience with assessment at home and follow up care	
The past year, a nurse has come by your house who asked you some questions about your health. What was your opinion about this visit at home by a nurse or research assistant? And what was done by you or the nurse with the results of this home visit? Probes: • What was your opinion about the questions the nurse asked you? • With whom were the results of the home-visit discussed (Think about caregiver, GP, specialist, physiotherapist, pharmacist) • What happened to your social/medical care provision after the home visit? • How did you act regarding your health after the home visit?	10 min
Experience shared decision-making	
How were decisions made regarding the care you received? Who was involved in these decisions?	10 min
Focus group topic guide professionals	
Introduction by the moderator:	
The past year you have been part of the research study Urban Health Centres Europe. This research project is a European project performed in five different countries, namely the United Kingdom, Spain, Greece, Croatia and the Netherlands. As part of this study your patients have received a home	5 min

visit with a health assessment by a nurse or health care provider. With the results of this house-visit the care he/she receives might have been changed. This focus group interview is part of the evaluation of the UHCE study. We would like to know your opinion and experiences with this program the past year. This focus group will last about 40-60 minutes. The focus group interview will be audio-taped and the researcher will transcript this into a written transcript at a later date for the purpose of analysis. The information will be used anonymous, no names will be mentioned. With the information you give us our aim is to develop a template for an Urban Health Centre Europe that will be characterized by integrated health and social care in the community for elderly. My role as a moderator is only to facilitate in a lively and productive discussion. I am interested in your personal opinions, so please feel free to express yourself. Do you have any questions about this? Do you agree with participation in this focus group discussion and tape-recording of this focus group discussion? [If everyone agrees start audio-tape] Richard fitton.	
Introduction participants	
• What is your profession?/background. • What was your role in UHCE? • Briefly tell me how the UHCe intervention was executed in Manchester, I mean the process. Who was involved etc.	5 min
General experience with the UHCE assessment and care past year	
What was your overall opinion of the UHCE assessment and care program the past year? What has the assessment and follow-up care done for the health or well-being of your patients? Probes: • What were the major strengths of this care program? • What were the barrriers of the program? • What improvements can be made to this care program? • Would you recommend assessing older persons 75+ years? Why/why not?	15 min
Experience with assessment at home and follow-up care	
What was you experience with the initial assessment at people's home? Probes: • Instruments appropriate? • Missed health problems? • Location at home? • Target group? What was your experience with the following-up care after this initial assessment? • With whom were the results of the house visit discussed? (Think about caregiver, GP, specialist, physiotherapist, pharmacist) • What happened to the social/medical care provision after the home visit? • How did your patient act regarding their health after the home visit? Reasons non-enrolment in care? How was the relationship between older persons and professionals? Did this influence whether/not persons participated? Its there continuity of UHCE in Manchester? Did something change after the program? Why/who not?	15 min
Integrated care and shared decision making	
What happened to the collaboration between you and other professionals in this program? How were decisions made regarding the care your patient received? How was participation medical/social care?	5 min

Supplementary Table S2 number of participants for the focus groups by city

	Older persons	Informal caregivers	Professionals	Professions
Pallini	4	1	4	Physician 2 Nurses Physical education teacher
Manchester	1st group 4 2nd group 4	1st group 1 2nd group 1	2	2 trained assistants
Valencia	5	0	5	General practitioner 2 Social workers Physical therapist Volunteer
Rijeka	5	0	6	4 Home care nurses Municipality officer Physician
Rotterdam	4	1	5	Occupational therapist Geriatric Nurse General practitioner Pharmacist Care manager
total	26	4	22	

PART

II

Health promotion for people with chronic conditions

6

Chapter 6

How to achieve better effect of peer support among adults with type 2 diabetes: A meta-analysis of randomized clinical trials

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ABSTRACT

Objectives To study the effects of peer support on glycemic control and examine effects of different providers and types of support, intervention duration and effect duration.

Methods A meta-analysis of randomized control trials (RCTs) of peer support intervention for patients with type 2 diabetes (T2DM) from beginning to November 3rd, 2014.

Results Twenty RCTs (n = 4494) were included. In general, peer support intervention (I^2 = 49.5%) had significantly positive effect on glycemic control of T2DM with pooled effect on HbA_{1c} of -0.16%, 95% CI -0.25 to -0.07% (-1.7mmol/mol, $P < 0.001$). Peer-partner-intervention and Community-health-worker-intervention had much better results of glycemic control. Home-visit-intervention and Curriculum-combined-reinforcement-intervention had better effect than other intervention types. The efficacy of interventions with duration>3&≤6 months was the best. However, effect weakens over time following intervention.

Conclusions Peer support is an effective measure of improving glycemic control for patients with T2DM. Different providers and types may have different effects on peer support. Peer support duration with the best metabolic effectiveness is >3&≤6 months.

Practice Implications Peer support provided by patients themselves or by nonprofessionals has significantly better effect, and Curriculum-combined-reinforcement-intervention and Home-visit-intervention are suggested. The duration should be >3&≤6 months. Further studies on the implementation of peer support are needed.

KEYWORDS Peer support; Type 2 Diabetes; Glycemic control; HbA_{1c}

INTRODUCTION

Diabetes mellitus is a chronic disease with significant morbidity and mortality which may result in long-term damage, dysfunction, and failure of organs such as retinopathy with potential loss of vision, nephropathy leading to renal failure, diabetic gangrene, and cardiovascular and cerebrovascular disease.[1] Furthermore, the prevalence rate of diabetes is increasing in countries around the world and the mortality of diabetes is also high.[2-4] There are several types of diabetes including type 1 diabetes, type 2 diabetes, gestational diabetes and other specific diabetes types.[5] Among all the patients with diabetes, about 90%–95% have type 2 diabetes which "encompasses individuals who have insulin resistance and usually have relative (rather than absolute) insulin deficiency".[1] The main characteristic of type 2 diabetes (T2DM) is hyperglycemia so that among patients with T2DM, the incidence of complications is strongly associated with the previous hyperglycemia.[6]

According to the results of trials, epidemiological analysis and meta-analysis, hyperglycemia commonly measured by glycated hemoglobin (HbA_{1c}) is significantly associated with the incidence of macro-vascular complications, the primary cause of death in patients with T2DM.[7] "Each 1% reduction in updated mean HbA1c was associated with reductions in risk of 21% for any end point related to diabetes, 21% for deaths related to diabetes, 14% for myocardial infarction, and 37% for microvascular complications".[6] Therefore, glycemic control is an important part of the treatment for patients with T2DM.

Patients with T2DM who want to control blood glucose effectively should make on-going changes in their lifestyle including diet, exercise, medication management and monitoring clinical and metabolic parameters which require strong self-management and self-regulation skills.[8] Thus, patients with T2DM need not only diabetes self-management education but also diabetes self-management support which could help them implement and sustain key behaviors in order to control their blood glucose.[9] Peer support, a kind of ongoing support from nonprofessionals, may effectively provide ongoing self-management support and help patients with diabetes change and sustain these key behaviors.[8, 10] One approach to defining peer support[10] identified four key functions of effective peer support as 1) assistance in daily management, 2) social and emotional support, 3) linkage to clinical care and community resources, and 4) ongoing availability of support. A guide developed by the Victorian Department of Human Services in Australia proposed seven types of peer support: Have a chat, Support groups, Internet and email peer support, Peer-led groups or events, Individual peer coaches, Telephone-based peer support, Community workers and Service provider-led groups.[11] As to the effect of peer support on glycemic control, there have been many studies on the relation between peer support and glycemic control effect among patients with T2DM but the results of different trials have not been altogether consistent. Additionally, there is no guideline for the implementation of peer support. Therefore, the purpose of this review is to study the effects of peer support on glycemic control for patients with T2DM and to identify important characteristics among providers, types, intervention duration and effect duration

through meta-analysis among relevant randomized control trials (RCTs).

METHODS

Data sources and searches

We searched Pubmed, ScienceDirect and Web of science to identify articles related to our study from their beginning to November 3rd, 2014. According to relevant definitions of peer support and the seven types of peer support, keywords used in searching were "type 2 diabetes", "T2DM", "self-management", "peer support", "peer group", "peer coach", "peer education" and "community health worker". We did not enclose the phrases used in searching in order to achieve a broad enough search scope. In addition, only articles published in English were considered. In Pubmed, we conducted searches in all fields and identified 352 articles. In both ScienceDirect and Web of science, we conducted searching in title/abstract/keywords and identified 52 articles from ScienceDirect and 30 from Web of Science after excluding duplicates. Details of the search syntax are in Supplementary Data.

We also examined the references in review articles like systematic reviews and meta-analysis to identify studies not captured through database searching. A systematic review on peer support covering 22 studies from Pubmed addressing peer support in diabetes published between January 1, 2000 and June, 2014 was included.[12] The review focused on the function and effect of peer support on several chronic diseases and searched more synonyms of peer support like *promotores*, doula, dumas and embajadores, therefore its search scope was broader than ours. We found 10 articles different from ours among these 22 and added them to our data sources.

Study selection

We only included original research of RCTs that studied the effect of peer support intervention for patients with T2DM and provided basic information and outcomes (e.g., mean and standard deviation of HbA_{1c} or relevant data from which we can derive the mean and standard deviation) which could be used to evaluate the effect on glycemic control. Moreover, only studies in which all or most subjects had type 2 diabetes were eligible. If the type of diabetes was unclear, then the study was included if the mean age of patients was more than 30 because most of these patients were likely to have type 2 diabetes. However, studies with subjects under 18 years old were excluded because peer support methods for adults are likely to be different from those for children and adolescents and this meta-analysis was intended to focus on T2DM among adults. In addition, studies with support intervention provided by professionals were excluded.

Of 444 articles with identified abstracts from Pubmed, ScienceDirect, Web of Science and references, we excluded 367 that were not original research (e.g., reviews, secondhand-data analysis, etc.); did not study the effect of peer support; did not provide relevant information on glycemic control; studied type 1 diabetes, gestational diabetes or other specific diabetes types; were not RCTs; studied patients under 18 years old; did not have qualified peer support

intervention (Fig.1). Two reviewers (Zhang and Yang) independently examined the full-text of the remaining 77 articles to identify eligible ones. Of the 77 articles, 56 were excluded because basic information and outcomes that could be used to evaluate the effect of glycemic control were missing (Fig.1). Among the remaining 21 articles, 20[13-32] were included in our meta-analysis study. One study[33] identified through Pubmed was excluded because the posttest results (mean of HbA_{1c}) of control group (CG) and intervention group (IG) were not accurate as the dropouts of IG were more than 20% without statistical tests to assess representativeness of those retained, and the attrition rate of IG was significantly higher than that of CG.

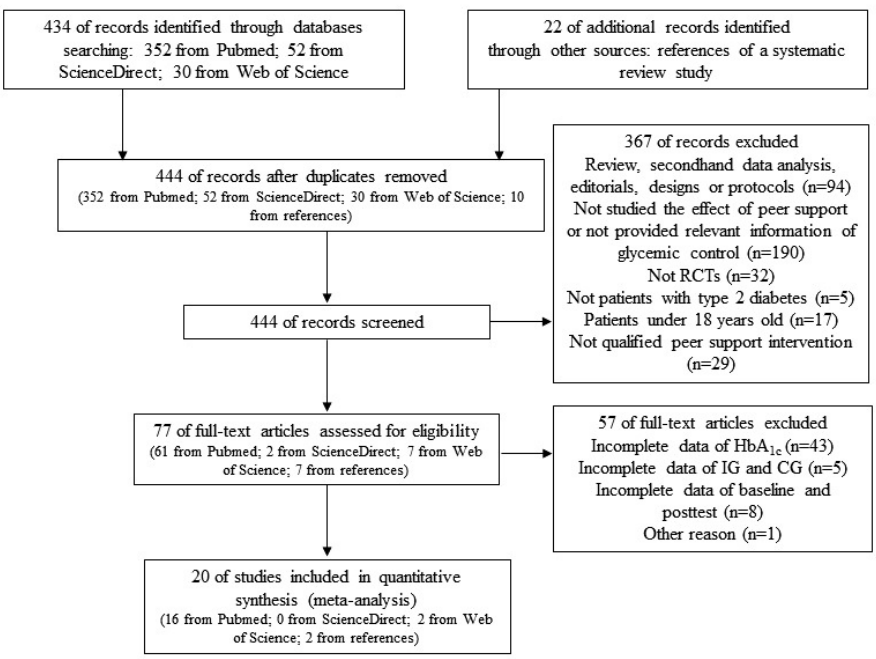

Figure 1 Flowchart of Study Selection

Data extraction and quality assessment

Data from the 20 eligible studies were extracted by one of the two reviewers (Zhang) with a standardized data extraction form and all the data extracted from the eligible studies were checked by another reviewer (Yang). The data extraction included: the first author's name, the year of publication, number of participants (including details of IG and CG at baseline and follow-up intervals separately, attrition and completion rate), participant characteristics (including types of patients, mean age, gender ratio, insulin usage and other features), study design, study location (country), intervention method, intervention duration, follow-up intervals and data of hemoglobin A1c (HbA_{1c}) values. Moreover, we numbered the eligible studies from 1 to 20.

As to the data of HbA_{1c} in each study, we extracted the mean and standard deviation (SD) of HbA_{1c} values of IG and CG at baseline and follow-up intervals separately, and most eligible studies only reported HbA_{1c} values as "%". Therefore, we used the NGSP's HbA_{1c} converter at http://www.ngsp.org/convert1.asp to calculate HbA_{1c} values as both % and mmol/mol. If the study only provided the mean changes of HbA_{1c} at follow-up intervals, then the mean values of IG and CG were calculated based on the mean changes and corresponding baseline mean of HbA_{1c} separately.[13, 21, 28, 31] What is more, if a study did not provide the SDs of mean values or data from which we can derive SDs at follow-up intervals, then we used corresponding baseline SDs as the follow-up interval SDs.[13, 21, 28, 31] If the study provided 95% Confidence Interval (CI) rather than SD of mean HbA_{1c} at baseline and follow-up intervals, then the SD values were calculated based on corresponding 95% CI separately.[14; 18; 19] One study[16] provided standard error (SE) rather than SD of mean HbA_{1c} at baseline and follow-up intervals. For this, we calculated the SD values based on corresponding SE values.

We classified the complexity of intervention methods in two ways: 1) we classified the intervention methods into 3 categories based on the providers of peer support, including Peer-leader-intervention (PLI – peer support intervention led by one or several peer coaches, peer leaders, peer educators, peer supporters or peer mentors who were usually also patients but had received relevant training), Community-health-worker-intervention (CHWI – intervention provided by nonprofessionals like community health workers, medical assistants, or community lay workers who had similar background or shared similar local culture with patients) and Peer-partner-intervention (PPI – intervention provided by patients themselves to help each other or to share experience together in a group, usually with no specific leader during the intervention); 2) we classified the intervention methods into 5 categories based on the approaches of peer support and setting, including Telephone-dominant-intervention (TDI – mainly providing peer support through regular telephone calls and sometimes combined with other methods like face-to-face contact), Support-group-intervention (SGI – mainly providing peer support through sharing experiences, setting goals and making plans and sometimes combined with relevant education at community setting), Home-visit-intervention (HVI – mainly providing peer support through home visits to educate the patients and help them to identify their difficulties and make plans to change their behaviors), Curriculum-only-intervention (CCOI – providing peer support through regular courses at community setting) and Curriculum-combined-reinforcement-intervention (CCRI – providing peer support through regular courses in combination with other regular interventions like telephone calls, postcards, face-to-face contact, support group meetings and home visits to reinforce the effect of curriculums).

We adopted the Cochrane Collaboration's tool for assessing risk of bias which includes six domains: selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias.[34] Two reviewers (Zhang and Yang) assessed each study independently and consulted Sun in the case of disagreements, all of which were then resolved by consensus.

Data analysis

The heterogeneity between studies was evaluated by I^2 test. If I^2 ≤50%, the possibility of heterogeneity between studies was low and fixed effect model could be utilized. If I^2 ≥50%, there was heterogeneity between studies and the sources of heterogeneity should be analyzed. We performed continuous data meta-analysis and adopted the weighted mean difference (WMD/MD) as the effect indicator. The criteria for significance is $P < 0.05$ and 95% CI not including 0. Sensitivity analysis was also performed to test the stability of the studies included. The possible publication bias was assessed by funnel plots with Begg and Egger tests with $P < 0.1$ as the criterion for significant publication bias. All statistical analyses were performed with Stata 11.0. GRADEpro 3.2 was utilized for the GRADE evidence strength assessment and table design.

RESULTS

Study selection and study characteristics

The twenty articles in the review included a total of 4494 participants (Fig. 1). Table 1 and 2 present the characteristics and HbA_{1c} results of each study. The number of participants of each study ranged from 46[27] to 628[17]. One study[27] only included female participants and one[26] only included male participants. All participants had type 2 diabetes in 16 studies[13-15, 17-20, 22-25, 27, 28, 30-32]. In the remaining 4 studies[16, 21, 26, 29], type of diabetes was unspecified but mean age was over 30 years old. In 3 studies[19, 24, 32], all participants were Mexican American. Two studies[21, 27] reported that participants were African American, and three[16, 31, 15] reported participants were Hispanic, Spanish-speaking or Latino adults. The intervention duration ranged from 1.25 months[16] to 24 months[14, 23]. Five studies[13, 15, 20, 24, 32] had more than one follow-up interval which ranged from -9[15] to 12 months[13]. Two studies[28, 30] also had more than one follow-up interval but we only included one interval of each study because of the quality of results. Most studies[14, 17-19, 21-23, 25-27, 29, 31] only had 0-month follow-up interval. One study[16] only had 1.75-month follow-up interval. Moreover, the details of intervention in IG and CG can be found in Supplementary Table S1.

Table 1 Characteristics of eligible studies included in meta-analysis

No., author, year	Number of participants	Participant Characteristics*	Study design, location	Intervention methods, duration
1, Thom, D. H., 2013 [18]	Baseline: In total: 299; IG: 148; CG: 151 Follow-up intervals† (0 month): Completion Rate (CR): 78.9%; IG: 122 Attrition: 17.6%; CG:114 Attrition: 24.5% (Patients who dropped out did not differ significantly from patients remaining in the study)	Patients: Type 2 diabetics with HbA1c level of 8.0% or greater within the past 6 months Mean age: 55 (range 29 to 82) Female (%): 52.2% Insulin usage (%): Baseline 55.0% Other features: Mostly low-income patients (<$10,000 per year)	RCT United States	PLI/TDI 6 months
2, Murrock, C. J., 2009 [27]	Baseline: In total: 46; IG: 24; CG: 22 Follow-up intervals (0 month): CR: 82.6%; IG: 20 Attrition: 16.7%; CG: 18 Attrition: 18.2%	Patients: Diagnosed type 2 diabetics with HbA1c level <10% within the past 6 months Mean age: 58.8 (IG) 67.1(CG) P<0.05 (There is significant difference in mean age between IG and CG, but no significant difference in the other dependent variables between IG and CG) Female (%): 100% Insulin usage (%): Baseline 21.7% Other features: African American women	RCT United States	PPI/SGI 3 months
3, Lorig, K., 2009 [28]	Baseline: In total: 345; IG: 186; CG: 159 Follow-up intervals (4.5 months): CR: 85.2%; IG: 161 Attrition: 15.5% ; CG: 133 Attrition: 16.4% Follow-up intervals (6 months for IG): 126 eligible CR: 81%; Attrition: 19%	Patients: Not pregnant or in care for cancer, and had type 2 diabetes. Participants' physicians verified their diagnoses. Mean age: 66.7 Female (%): 66% Insulin usage (%): Baseline 17.4% Other features: The DSMP intervention participants were followed for an additional 6 months (12 months total)	RCT United States	PLI/CCOI 1.5months
4, Lujan, J., 2007 [32]	Baseline: In total: 150; IG: 75; CG: 75 Follow-up intervals (-3 months): CR: 95.3%; IG: 73 Attrition: 2.7% ; CG: 70 Attrition: 6.7% Follow-up intervals (0 month): CR: 94%; IG: 71 Attrition: 5.3%; CG: 70 Attrition: 6.7%	Patients: Diagnosed with type 2 diabetes for at least 1 year Mean age: 58 Female (%): 80% Insulin usage (%): --; 96% hypoglycemic agents Other features: Mexican American	RCT Texas-Mexico Border	CHWI/CCRI 6 months
5, Duggan, C., 2014 [16]	Baseline: In total: 320 IG: 154 CG: 166 Follow-up intervals (1.75months)‡: CR: 100%; IG: 154 Attrition: 0%; CG: 166 Attrition: 0%	Patients: HbA1c higher than 6%; 67.3% diagnosed with diabetes Mean age: 50.6 Female (%): 70.6% Insulin usage (%): Baseline 18.3% Other features: Hispanics	RCT United States	CHWI/ HVI 1.25 months

6 Cade, J. E., 2009 [30]	Baseline(with HbA_{1c} data): In total: 207; IG: 89; CG: 118 Follow-up intervals (10.25 month, with HbA_{1c} data)[§]: CR: 79.2%; IG: 86 Attrition: 3.4%; CG: 108 Attrition: 8.5%	Patients: Adults with Type 2 diabetes (defined as onset over age 30 years, not on insulin within the first year) Mean age: IG: 65.4 CG: 66.2 Female (%): 41.3% Insulin usage (%): 0% Other features: Registered with GP practices selected from socially deprived catchment areas	RCT UK	PLI/CCOI 1.75 months
7, Gagliardino, J. J., 2013 [20]	In total: 198; IG: 93; CG: 105 Baseline(with HbA_{1c} data): IG:66; CG:78 Follow-up intervals (-6 months, with HbA_{1c} data): CR: 99.5%; IG: 92 Attrition: 1.1% ; CG: 105 Attrition: 0% Follow-up intervals (0 month, with HbA_{1c} data): IG: 93 Attrition: 0%; CG: 104 Attrition: 0.10%	Patients: People with type 2 diabetes for at least 2 years with more than two diabetes encounters Mean age: IG:62 CG:60 Female (%): 51.4% Insulin usage (%): -- Other features: Patients were selected from a list of people with type 2 diabetes provided by physicians	RCT Argentina	PLI/CCRI 12 months
8, Lorig, K., 2008 [31]	Baseline[||]: In total: 417; IG: 219; CG: 198 Follow-up intervals (0 month): CR: 84.4%; IG: 179 Attrition: 18.3%; CG: 173 Attrition: 12.6%	Patients: Not pregnant or in care for cancer, and had type 2 diabetes Mean age: 52.9 Female (%): IG: 57.1% CG: 67.2% P=0.034<0.05[¶] Insulin usage (%): Baseline 10.3% Other features: Spanish-speaking adults	RCT United States	PLI/CCRI 6 months
9, Smith, S. M., 2011 [23]	Baseline(with HbA_{1c} data): In total: 388; IG: 187; CG: 201 Follow-up intervals (0 month, with HbA_{1c} data): CR: 86.3%; IG: 165 Attrition: 11.8%; CG: 170 Attrition: 15.7%	Patients: Had type 2 diabetes, be able to participate in a group, and be attending one of the participating practices Mean age: IG:66.1 CG:63.2 Female (%): 45.8% Insulin usage (%): 2% Other features: --	RCT (cluster) Ireland	PLI/SGI 24 months
10, Philis-Tsimikas, A., 2011 [24]	Baseline: In total: 207; IG: 104; CG: 103 Follow-up intervals (0 month, with HbA_{1c} data): CR: 70.0%; IG: 64 Attrition: 38.5%; CG: 81 Attrition: 21.4% Follow-up intervals (6 months, with HbA_{1c} data): CR: 64.3%; IG: 56 Attrition: 38.5%; CG: 74 Attrition: 21.4% Participants who were lost to follow-up did not differ significantly from those who completed at least one assessment on any demographic or outcome variable.	Patients: With type 2 diabetes and HbA1c>10% Mean age: IG: 52.2 CG: 49.2 P=0.05 No significant difference in the other dependent variables between IG and CG Female (%): 70.5% Insulin usage (%): -- Other features: High-Risk Mexican Americans	RCT United States	PLI/CCRI 4 months

11, Dale, J., 2009 [29]	Baseline[#]: In total: 187; IG: 90; CG: 97 Follow-up intervals (0 month, with HbA_{1c} data): CR: 87.7%; IG: 78 Attrition: 13.3%; CG: 86 Attrition: 11.3%	Patients: Patients with a recent HbA1c greater than 7.4% Mean age: IG: Under 50 (19.3%) 51-59 (52.3%) Over 70 (28.4%); CG: Under 50 (13.5%) 51-59 (60.7%) Over 70 (25.8%) Female (%): 60.0% Insulin usage (%): 0% Other features: Patients should have a telephone and have the ability to communicate over the phone with adequate English.	RCT UK	PLI/TDI 6 months
12, Prezio, E. A., 2013 [19]	Baseline: In total: 180; IG: 90; CG: 90 Follow-up intervals (0 month): CR: 86.7%; IG: 78 Attrition: 13.3%; CG: 78 Attrition: 13.3%	Patients: Diagnosed with type 2 diabetes treated with oral agents, insulin or no medications; not pregnant Mean age: IG: 47.9 CG: 45.7 Female (%): 60.6% Insulin usage (%): -- Other features: Uninsured Mexican Americans	RCT United States	CHWI/SGI 12 months
13, Perez-Escamilla, R., 2014 [15]	Baseline: In total: 211; IG: 105; CG: 106 Follow-up intervals (-9 month): CR: 84.8%; IG: 92 Attrition: 12.4%; CG: 87 Attrition: 17.9% Follow-up intervals (-6 month): CR: 80.1%; IG: 86 Attrition: 18.1%; CG: 83 Attrition: 21.7%[**] Follow-up intervals (0 month): CR: 74.4%; IG: 82 Attrition: 21.9%[**]; CG: 75 Attrition: 29.2%[**] Follow-up intervals (6 months): CR: 70.1%; IG: 79 Attrition: 24.8%[**]; CG: 69 Attrition: 34.9%[**]	Patients: Had a documented diagnosis of type 2 diabetes for >12 months; not pregnant; no cancer Mean age: 56.3 Female (%): 73.5% Insulin usage (%): -- Other features: Latino adults	RCT United States	CHWI/HVI 12 months
14, Baghiani moghadam, M. H., 2012 [22]	Baseline: In total: 80; IG: 40; CG: 40 Follow-up intervals (0 month): CR: 100%; IG: 40 Attrition: 0%; CG: 40 Attrition: 0%	Patients: Had type 2 diabetes, were using blood sugar decreasing drugs Mean age: IG: 47.7 CG: 50.3 Female (%): 82.5% Insulin usage (%): -- Other features: Absence of cardiovascular complications, diabetic foot or any other problems that prevent patients to do walking	RCT Iran	PLI/SGI 3 months
15, Rothschild, S. K., 2014 [14]	Baseline: In total: 144; IG: 73; CG: 71 Follow-up intervals (0 month): CR: 84%; IG: 59 Attrition: 19.2%; CG: 62 Attrition: 12.7%	Patients: Had type 2 diabetes and were being treated with at least 1 oral hypoglycemic agent Mean age: 53.7 Female (%): 67.4% Insulin usage (%): -- Other features: Mexican Americans in metropolitan Chicago	RCT United States	CHWI/HVI 24 months

16, Ruggiero, L., 2010 [25]	Baseline: In total: 50; IG: 25; CG: 25 Follow-up intervals (0 month): CR: 84%; IG: 24 Attrition: 4%; CG: 18 Attrition: 28% (There were no significant difference between IG and CG before and after the intervention.)	Patients: Diagnosis of type 2 diabetes for at least one year, last two HbA1c≥7%, prescribed diabetes medication Mean age: 65.8 Female (%): 66% Insulin usage (%): -- Other features: Latino or African American	RCT United States	CHWI/CCRI 6 months
17, Long, J. A., 2012 [21]	Baseline (with HbA_{1c} data)[††]:In total: 77; IG: 38; CG: 39 Follow-up intervals (0 month, with HbA_{1c} data): CR: 98.7%; IG: 37 Attrition: 5.1%; CG: 39 Attrition: 0%	Patients: Aged 50 to 70 years with persistently poor diabetes control Mean age: 60 Female (%): 5% Insulin usage (%): -- Other features: Self-identified race of black or African American	RCT United States	PLI/TDI 6 months
18, Tang, T. S., 2014 [13]	Baseline: In total: 116; IG: 60; CG: 56 Follow-up intervals (0 month, with HbA_{1c} data): CR: 82.8%; IG: 49 Attrition: 18.3%; CG: 47 Attrition: 16.1% Follow-up intervals (6 month, with HbA_{1c} data): CR: 71.6%; IG: 42 Attrition: 39%; CG: 41 Attrition: 26.8% Follow-up intervals (12 month, with HbA_{1c} data): CR: 59.5%; IG: 37 Attrition: 38.3%; CG: 32 Attrition: 42.9% (Loss to follow-up was not different between the two groups and was not associated with clinical or demographic variables)	Patients: Receiving medical care at CHASS with physician-diagnosed type 2 diabetes Mean age: 49.3 Female (%): 52% Insulin usage (%):Baseline 26% Other features: Self-identified as Latino	RCT United States	PLI/CCRI 6 months
19, Chan, J. C. N., 2014 [17]	Baseline: In total: 628; IG: 312; CG :316 Follow-up intervals (0 month):CR: 93.3%; IG: 296 Attrition: 5.1%; CG: 290 Attrition: 8.2%	Patients: Had type 2 diabetes, underwent comprehensive assessments and expressed willingness to participate Mean age: 54.7 Female (%): 43.5% Insulin usage (%):Baseline 28.8% Other features: --	RCT China HK	PLI/TDI 12 months
20, Heisler, M., 2010 [26]	Baseline: In total: 244; IG: 125; CG :119 Follow-up intervals (0 month, with HbA_{1c} data): CR: 88.5%; IG: 113 Attrition: 9.6%; CG: 103 Attrition: 13.4%	Patients: Diabetes patients with HbA1c in the prior 6 months of 7.5% or more Mean age: IG:61.8 CG:62.3 Female (%): 0% Insulin usage (%): -- Other features:--	RCT United States	PPI/CCRI 6 months

[*] If there is no special explanation, there are no significant differences in the demographic characteristics and dependent variables between IG and CG. Mostly, the content of characteristics is the description of all the participants in both IG and CG. If they were described separately, there would be labels of IG and CG.

† Follow-up is from the end of the intervention; follow-up of 0 month means that the measurement occurred immediately at the end of the intervention; follow-up of -3 months means that the measurement occurred during the intervention and there are still 3 months intervention left.

‡ The study had same 6-month intervention for both IG and CG. CG received 3-month delayed intervention, so we only included the first 3 months results as there was a control group with usual care in the first 3 months.

§ 6-month results were also presented in the study but the results were not good because the attrition of participants of CG was far more than 20% without statistical explanation. Therefore, we only used results of 12-month.

|| This article reports on two studies 1) a randomized 6-month trial of the SDSMP, with an 18-month longitudinal follow-up, and 2) an18-month randomized comparison of automated telephone reinforcement of the SDSMP versus the nonreinforced SDSMP which aimed at testing the effect of automated telephone reinforcement on maintaining the effect of SDSMP. Therefore, we only used the results of the first study which aimed at testing the effect of SDSMP on glycemic control for diabetics. As to the 18-month longitudinal follow-up in the first study, the results of participants from IG and CG were not presented separately, so we didn't used the follow-up results.

¶ There was a significant difference in the percentage of female participants between IG and CG and only outcome with significant baseline difference was activity limitation (P=0.036), but no significant difference in the other dependent variables between IG and CG

In this study, there were two intervention groups, DSN and PS. The intervention method of DSN was telecare support provided by diabetes specialist nurses while the method of PS was telecare support supporters. Therefore, we only used the results of PS to be the results of intervention group and the information of DSN was not presented in the table.

** Participants who were lost to follow-up were similar to those who completed in baseline characteristics except the marriage and cell phone owning situation. Completers were more likely to have a cell phone ((68.9% vs. 54%, P =0.038) and were less likely to be married (18.2% vs. 31.7%, P = 0.013)

†† In this study, there were two intervention groups, peer mentor and financial incentives. We only used the results of peer mentor as the results of the intervention group.

Table 2 HbA_{1c} values and related data of intervention group (IG) and control group (CG) at baseline and follow-up intervals

Study	Baseline HbA1c % (mmol/mol)						Intervention duration (months)	Follow-up intervals (months)	Follow-up HbA1c % (mmol/mol)					
	IG			CG					IG			CG		
	N	Mean	SD	N	Mean	SD			N	Mean	SD	N	Mean	SD
1 [18]	148	10.14 (87)	2.01 (22)	151	9.84 (84)	1.95 (21.3)	6	0	122	8.98 (75)	2 (21.9)	114	9.55 (81)	2.30 (25.1)
2 [27]	24	7.70 (61)	1.20 (13.1)	22	7.40 (57)	1.10 (12)	3	0	20	7.20 (55)	1.10 (12)	18	7.70 (61)	1.40 (15.3)
3 [28]	186	6.70 (50)	1.48 (16.2)	159	6.74 (50)	1.38 (15.1)	1.5	4.5[†]	161	6.59 (49)	1.48 (16.2)	133	6.57 (48)	1.38 (15.1)
4 [32]	75	8.21 (66)	2.20 (24.0)	75	7.71 (61)	1.49 (16.3)	6	-3	73	7.75 (61)	2.00 (21.9)	70	7.84 (62)	1.70 (18.6)
								0	71	7.76 (61)	1.87 (20.4)	70	8.01 (64)	1.80 (19.7)
5 [16]	154	8.04 (64)	2.11 (23.1)	166	8.31 (67)	1.67 (18.3)	1.25	1.75	154	7.68 (60)	1.37 (15.0)	166	7.59 (59)	1.67 (18.3)
6 [30]	89	7.30 (56)	1.30 (14.2)	118	7.50 (58)	1.40 (15.3)	1.75	10.25	86	7.60 (60)	1.20 (13.1)	108	7.60 (60)	1.30 (14.2)
7 [20]	66	7.10 (54)	1.50 (16.4)	78	7.30 (56)	1.50 (16.4)	12	-6	92	6.60 (49)	0.90 (9.8)	105	7.00 (53)	1.10 (12.0)
								0	93	6.80 (51)	1.30 (14.2)	104	7.00 (53)	1.10 (12.0)
8 [31]	219	7.44 (58)	2.00 (21.9)	198	7.38 (57)	1.87 (20.4)	6	0	179	7.03 (53)	2.00 (21.9)	173	7.33 (57)	1.87 (20.4)
9 [23]	187	7.20 (55)	1.40 (15.3)	201	7.20 (55)	1.20 (13.1)	24	0	165	7.10 (54)	1.10 (12.0)	170	7.10 (54)	1.20 (13.1)
10 [24]	104	10.50 (91)	1.70 (18.6)	103	10.30 (89)	1.70 (18.6)	4	0	64	9.00 (75)	1.90 (20.8)	81	9.10 (76)	1.90 (20.8)
								6	56	9.10 (76)	2.00 (21.9)	74	9.70 (83)	2.30 (25.1)
11 [29]	90	8.40 (68)	1.10 (12.0)	97	8.70 (72)	1.30 (14.2)	6	0	78	8.00 (64)	1.50 (16.4)	86	7.90 (63)	1.10 (12.0)
12 [19]	90	8.80 (73)	1.45 (15.8)	90	8.80 (73)	1.45 (15.8)	12	0	78	7.20 (55)	1.35 (14.8)	78	7.90 (63)	1.58 (17.3)
13 [15]	105	9.70 (83)	2.09 (22.8)	106	9.76 (83)	2.23 (24.4)	12	-9	92	8.77 (72)	2.03 (22.2)	87	9.19 (77)	2.29 (25.0)
								-6	86	8.81 (73)	2.11 (23.1)	83	9.28 (78)	1.76 (19.2)
								0	82	8.85 (73)	1.76 (19.2)	75	9.42 (79)	1.54 (16.8)
								6	79	8.77 (72)	1.93 (21.1)	69	9.32 (78)	1.76 (19.2)
14 [22]	40	7.02 (53)	0.58 (6.3)	40	6.91 (52)	0.54 (5.9)	3	0	40	6.10 (43)	0.60 (6.6)	40	6.14 (44)	0.64 (7.0)
15 [14]	73	8.35 (68)	1.26 (13.8)	71	8.23 (66)	1.22 (13.3)	24	0	59	7.64 (60)	1.10 (12.0)	62	8.33 (68)	1.14 (12.5)
16 [25]	25	8.90 (74)	1.59 (17.4)	25	8.45 (69)	1.71 (18.7)	6	0	24	8.73 (72)	1.74 (19.0)	18	8.50 (69)	2.25 (24.6)
17 [21]	38	9.80 (84)	1.80 (19.7)	39	9.90 (85)	1.60 (17.5)	6	0	37	8.72 (72)	1.80 (19.7)	39	9.89 (85)	1.60 (17.5)
18 [13]	60	8.20 (66)	2.20 (24.0)	56	7.80 (62)	1.70 (18.6)	6	0	49	7.50 (58)	2.20 (24.0)	47	7.30 (56)	1.70 (18.6)
								6	42	7.60 (60)	2.20 (24.0)	41	7.40 (57)	1.70 (18.6)
								12	37	7.60 (60)	2.20 (24.0)	32	7.50 (58)	1.70 (18.6)
19 [17]	312	8.20 (66)	1.70 (18.6)	316	8.20 (66)	1.60 (17.5)	12	0	296	7.90 (63)	1.53 (16.7)	290	7.91 (63)	1.51 (16.5)
20 [26]	125	8.02 (64)	1.32 (14.4)	119	7.93 (63)	1.40 (15.3)	6	0	113	7.73 (61)	1.32 (14.4)	103	8.22 (66)	1.74 (19.0)

[†]The 10.5 months follow-up of this study was for IG only, therefore we did not included the results of 10.5 months follow-up in this meta-analysis.

Risk of bias

All 20 studies included in our meta-analysis were RCTs, but only one study[26] reported blinding of participants and personnel. Individual quality of most studies revealed low bias risk in most domains (Supplementary Table S2).

Quality of the evidence for most results in our study was from moderate to high, except the results of PPI, CCOI and Follow-up >6 months after the end of intervention due to limited studies (Supplementary Table S3).

Overall results of peer support intervention effect

All 20 studies provided related data of HbA_{1c} mean and HbA_{1c} SD as the outcome measure of peer support intervention effect. In 17 studies[13-15, 17-27, 29, 31, 32], we used the HbA_{1c} results of 0 month follow-up to represent the effect of intervention. However, 3 studies[16, 28, 30] only provided the results of 1.75-month follow-up, 4.5-month follow-up and 10.25 follow-up respectively. We used these results of the 3 studies to represent the effect of intervention. Figure 2, Part A presented the combined results of the 20 studies in our meta-analysis. The results showed heterogeneity between studies (I^2 = 49.5%) was acceptable. The pooled results indicated statistically significant difference in HbA_{1c} outcomes between IG and CG of -0.16% (95% CI -0.25 to -0.07) or -1.7mmol/mol (P < 0.001). The sensitivity of 20 studies was low and the publication bias was acceptable. The details of sensitivity analysis and publication bias assessment can be found in Supplementary Data.

Results of subgroup analysis based on intervention duration

We divided the results into three mutually exclusive groups (≤3 months, >3&≤6 months, ≥12 months) based on the intervention duration (no studies reported duration >6&<12 months) to perform the subgroup analysis (Fig. 2, Part B). In intervention duration ≤3 months group[16, 22, 27, 28, 30], although there was no heterogeneity (I^2 = 0%), the difference in HbA_{1c} outcomes between IG and CG of -0.01% (95% CI -0.16 to 0.15) or -0.1mmol/mol was much smaller and no longer statistically significant (P = 0.924). In the group of studies with duration >3&≤6 months[13, 18, 21, 24-26, 29, 31, 32], the heterogeneity was reduced (I^2 = 38.4%) and there were larger differences in HbA_{1c} outcomes with statistical significance -0.28% (95% CI -0.46 to -0.09) or -3.1mmol/mol (P = 0.003). Similarly, among the group with duration ≥12 months group[14, 15, 17, 19, 20, 23], difference in HbA_{1c} was greater, -0.21% (95% CI -0.34 to -0.07) or -2.3mmol/mol (P = 0.002), but the heterogeneity increased substantially (I^2 = 70.7%). Moreover, although there was no statistically significant difference among the three groups, the P value of heterogeneity among the three groups was 0.057 which was close to 0.05.

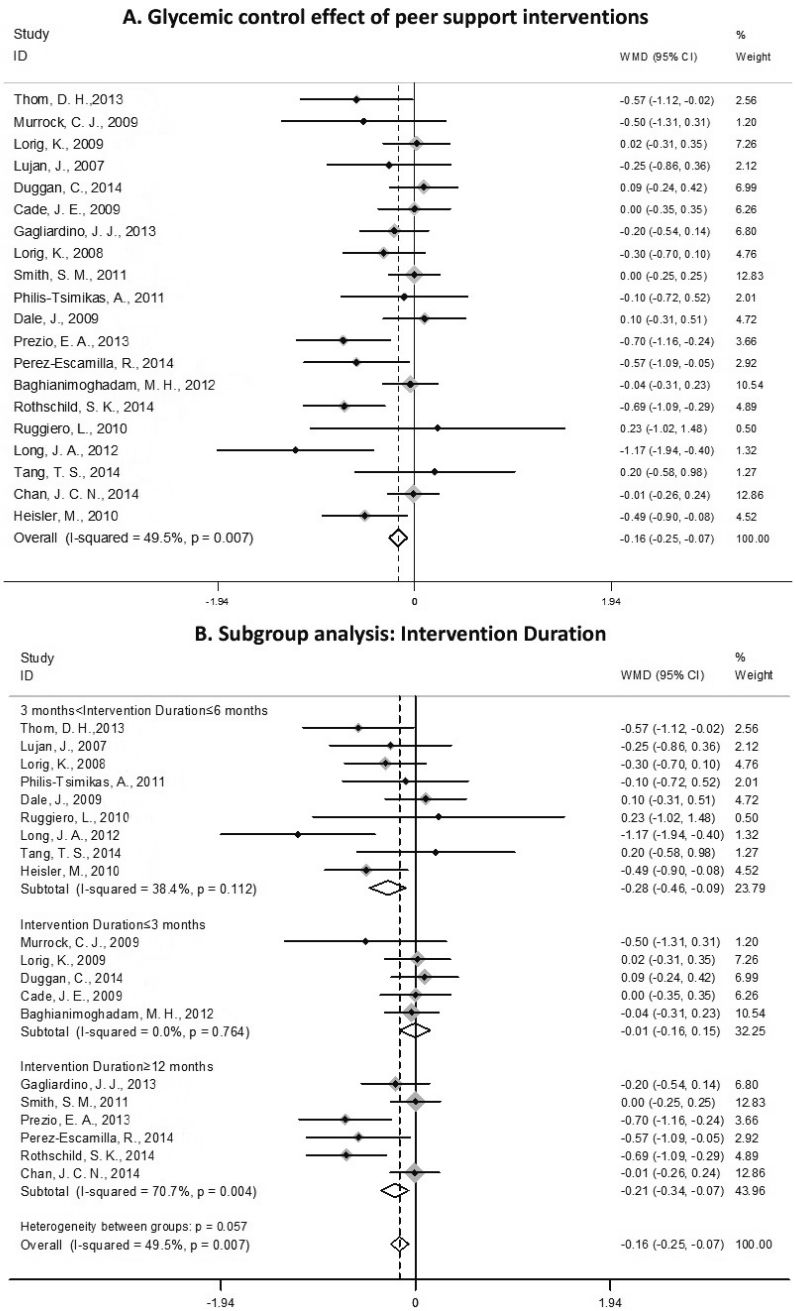

Figure 2 Forest plots

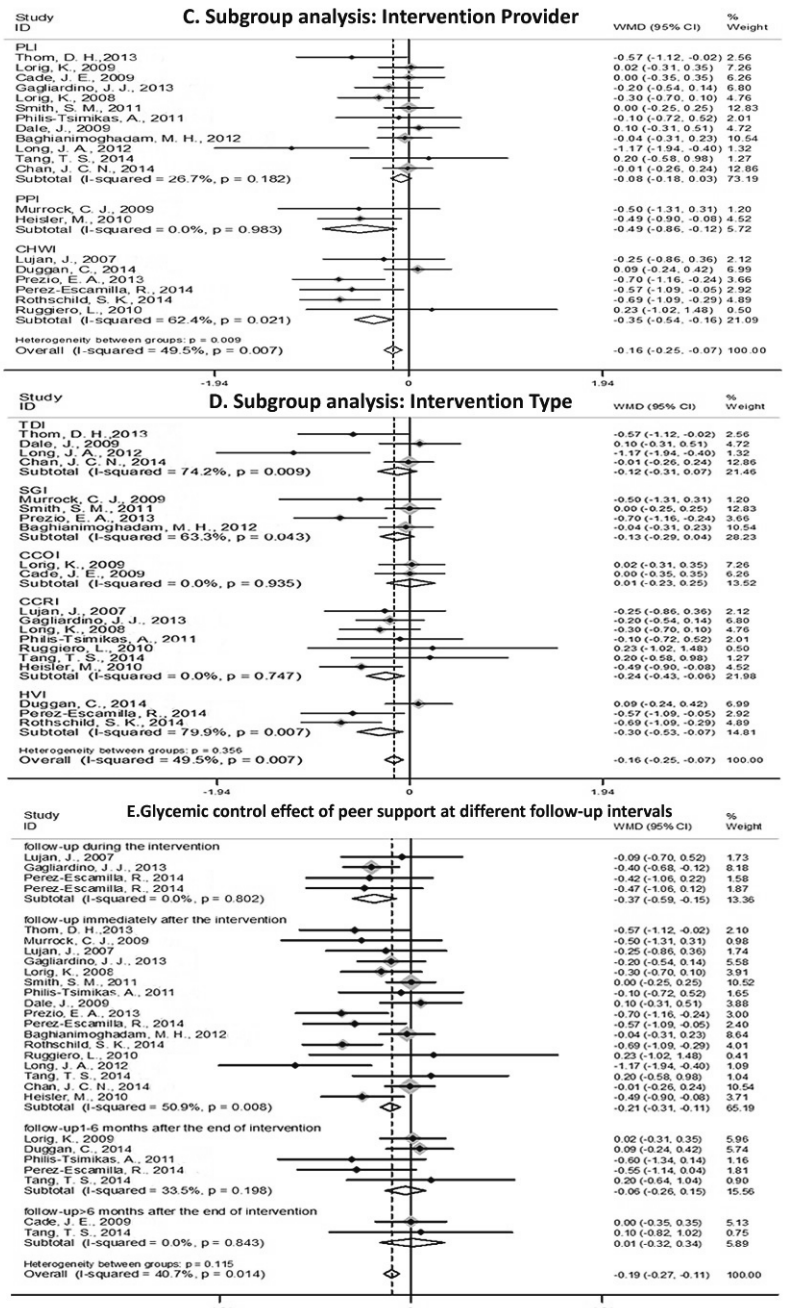

Figure 2 Forest plots (Continued)

Results of subgroup analysis based on intervention provider

Based on intervention provider, we divided the studies into three groups, PLI, PPI and CHWI (Fig. 2, Part C). In the PLI group[13, 17, 18, 20-24, 28-31], we found heterogeneity reduced (I^2 = 26.7%) but the difference in HbA_{1c} outcomes between IG and CG was smaller and no longer statistically significant (-0.08%, 95% CI -0.18 to -0.03, or -0.9mmol/mol, P = 0.141). In the PPI group, the difference in HbA_{1c} outcomes of -0.49% (95% CI -0.86 to -0.12) or -5.4mmol/mol (P = 0.009) was much larger and without heterogeneity (I^2 = 0%). There were, however, only two studies[26, 27] in this group. In the CHWI group[14-16, 19, 25, 32], there was larger difference in HbA_{1c} outcomes of -0.35% (95% CI -0.54 to -0.16) or -3.8 mmol/mol (P < 0.001) but the heterogeneity increased substantially (I^2 = 62.4%). Additionally, there was statistical significant difference among these three groups (P = 0.009).

Results of subgroup analysis based on intervention type

The subgroup analysis also examined intervention type (TDI, SGI, CCOI, CCRI and HVI, see Fig. 2, Part D). Results indicated nonsignificant differences in HbA_{1c} outcomes between IG and CG in both the TDI group[17, 18, 21, 29] (-0.12%, 95% CI -0.31 to 0.07, or -1.3mmol/mol, P = 0.202) and the SGI group[19, 22, 23, 27] (-0.13%, 95% CI -0.29 to 0.04, or -1.4mmol/mol, P = 0.134) with substantial heterogeneity respectively (I^2 = 74.2%; I^2 = 63.3%, respectively). In the CCRI group[13, 20, 24-26, 31, 32], there was no heterogeneity (I^2 = 0%) and the pooled results showed larger statistical significant difference in HbA_{1c} outcomes of -0.24% (95% CI -0.43 to -0.06), or -2.6mmol/mol (P = 0.011). Combining results of HVI group[14-16], there was also a larger difference in HbA_{1c} outcomes of -0.30% (95% CI -0.53 to -0.07), or -3.3mmol/mol (P = 0.011) but the heterogeneity increased substantially (I^2 = 79.9%). In the CCOI group[28, 30], the difference in HbA_{1c} outcomes between IG and CG was 0.01% (95% CI -0.23 to 0.25), or 0.1mmol/mol (P = 0.93). These five groups did not differ significantly from each other (P = 0.356).

Results of peer support intervention at different follow-up intervals

We also combined all the results of 28 follow-up intervals of 20 studies in meta-analysis (Fig. 2, Part E). The overall pooled results of 28 follow-up intervals indicated statistically significant difference in HbA_{1c} outcomes between IG and CG of -0.19% (95% CI -0.27 to -0.11), or -2.1mmol/mol (P <0.001) with acceptable heterogeneity (I^2 = 40.7%). We divided the 28 follow-up intervals into four groups (follow-up during the intervention, immediately after the intervention, >1&≤6 months after the end of intervention, >6 months after the end of intervention) for subgroup analysis. For HbA_{1c} measured immediately after the intervention[13-15, 17-27, 29, 31, 32], the heterogeneity increased (I^2 = 50.9%) and the pooled results indicated larger difference in HbA_{1c} outcomes between IG and CG of -0.21% (95% CI -0.31 to -0.11), or -2.3mmol/mol (P < 0.001). For HbA_{1c} measured during the intervention[15, 20, 32], we found larger difference in HbA_{1c} outcomes of -0.37% (95% CI -0.59 to -0.15), or -4.0mmol/mol (P = 0.001) without heterogeneity (I^2 = 0%). For HbA_{1c} measured at >1&≤6 months after the end of intervention[13, 15, 16, 24, 28], the heterogeneity was reduced (I^2 = 33.5%) but the difference in HbA_{1c} outcomes of -0.06% (95% CI -0.26 to 0.15), or -0.7mmol/mol (P = 0.585) was not

significant. For HbA_{1c} measured >6 months after the end of intervention[13, 30], we found no heterogeneity (I^2 = 0%) but there was opposite result that the difference in HbA_{1c} outcomes between IG and CG was 0.01% (95% CI -0.32 to 0.34), or 0.1mmol/mol without statistical significance (P = 0.939). The differences among these four groups were not significant (P = 0.115).

DISCUSSION AND CONCLUSIONS

Discussion

Peer support interventions have significantly positive effect on glycemic control for patients with T2DM with pooled effect on HbA1c of -0.16% (95% CI -0.25 to -0.07) or -1.7mmol/mol (P < 0.001) and acceptable heterogeneity among studies (I^2 = 49.5%). As mentioned in the Introduction, a 1% reduction in HbA1c has been associated with "reductions in risk of 21% for any end point related to diabetes, 21% for deaths related to diabetes, 14% for myocardial infarction, and 37% for microvascular complications".[6] Therefore, the effect of peer support on glycemic control is important for the treatment of patients.

The differences of peer support providers may influence the effect of peer support. There is significant difference in outcomes (P = 0.009) among the three categories of providers. Peer-partner-intervention demonstrates significantly positive effect with the best HbA_{1c} outcome of -0.49% (95% CI -0.86 to -0.12) or -5.4mmol/mol (P = 0.009). Community-health-worker-intervention also achieves an impressive pooled effect of -0.35% (95% CI -0.54 to -0.16) or -3.8 mmol/mol (P < 0.001). For Peer-leader-intervention, however, the difference between control and intervention conditions was not significant (P = 0.141).

There may be a number of reasons for these differences by type of peer provider. In Peer-partner-intervention, participants may have better self-regulation ability because each patient has to be able to implement as well as receive the intervention. Those receiving Community-health-worker-intervention may be managed or educated better than those receiving Peer-leader-intervention because nonprofessionals providing Community-health-worker-intervention are more skilled and responsible than specific patient leaders. However, it is important to note that these differences by provider were based on small numbers of studies (e.g., only 2 in Peer-partner-intervention category). Also, because of the small numbers of studies, other characteristics (e.g., age, sex, baseline characteristics) were not controlled in statistical analyses. Therefore, the differences by provider should be taken as tentative, a basis for further research, not a firm basis for programmatic decisions.

Turning to the types of peer support, differences among categories were not significant. Curriculum-combined-reinforcement-intervention and Home-visit-intervention achieve significant positive effects on glycemic control relative to control conditions. Although not significant, the observed positive benefit of Telephone-dominant-intervention is consistent with a previous systematic review and meta-analysis which found effects of phone-call-intervention on glycemic control in 5 trails with 953 diabetes patients.[35]

According to the subgroup analysis of intervention duration, interventions ≤3 months has no significant positive effect on glycemic control. Both interventions >3&≤6 months and interventions ≥12 months have significant positive effect, and the effect of interventions >3&≤6 months is greater than that of interventions ≥12 months. The better effect of interventions lasting >3 months confirms the finding of a previous review[36] of self-management interventions in diabetes that identified duration of intervention as major determinant of impact on HbA_{1c}. Therefore, the intervention duration with the best effect is >3&≤6 months. Among all the studies included, however, we found no study with intervention duration >6&<12 months. The high heterogeneity among the group of interventions with duration ≥12 months and the current finding of somewhat greater benefits of intervention lasting >3&≤6 months relative to those lasting ≥12 months indicate that we still need more studies on peer support duration for further research.

In addition, the effect of peer support on glycemic control weakens over time. According to the results measured during/immediately after the intervention, the effect is significantly positive and the efficacy during the intervention is better than that immediately after the intervention. The effect of peer support measured at ≤6 months follow-up interval is still positive but nonsignificant, while the efficacy measured at >6 months follow-up interval is negative without significance, indicating more attention should be paid to maintain the effect of peer support after the end of intervention and we need to provide ongoing support. However, more studies should examine ongoing support, including specific time points and reinforcement methods.[37]

There are still some limitations in our meta-analysis. Firstly, although the 20 studies included are RCTs, of which 19 studies are not double blinded. Secondly, the control groups of some studies not only adopted usual care but also some additional interventions like education, appointments or follow-up visits which may have compromised the sensitivity of studies to detect true effects of peer support. Thirdly, some subgroups in our subgroup analyses have small number of studies, some have high heterogeneity, and some have both. Fourthly, we did not conduct subgroup analysis controlling for other influencing factors of peer support like intervention intensity because of the limited studies.

Conclusions

In summary, peer support in these 20 studies achieves modest but statistically significant benefits on glycemic control for patients with T2DM. Analyses suggest possible differences among providers and type of peer support. Duration >3&≤6 months is more likely effective and the effect of peer support on glycemic control weakens over time especially after the end of intervention. Both of them point to the importance of ongoing support and the importance of research investigating it such as through reinforcement methods within 6 months after the end of intervention.

Practice Implications

Peer support programs for diabetes should be extended. Peer support provided by patients themselves as a group or provided by nonprofessionals like community workers may have significantly better effect. Other suggestions from the present subgroup analyses include that the advantages of Curriculum-combined-reinforcement-intervention and Home-visit-intervention, duration of peer support should last >3&≤6 months, and ways to provide ongoing support should be developed. Moreover, more studies are needed to verify the results of our subgroup analyses or to study several subgroups with high heterogeneity in our analyses (e.g. Telephone-dominant-intervention and Home-visit-intervention). In addition, peer support should be studied explicitly from the aspects of its providers, types, intervention location, intensity, duration of intervention, duration of effect, behavior theories, cost-effectiveness, etc.

Peer support is complicated and could be influenced by many factors like culture, psychology, emotion and social environment. Therefore, it is necessary to take these contextual factors into consideration to implement peer support. However, there is little systematic study on peer support to provide theoretical guidelines.[38] Many problems need to be resolved, for example, “What kind of peer support should we choose when we want to intervene in specific populations or achieve specific targets?” “What is the best way of expressing or teaching in the process of peer support to help patients change their behavior?” “How should we train and manage the peer supporters?” “What is the long-term influence of peer support on peer support providers?” and “What is the negative influences of peer support on patients?” etc.

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Search Syntax:

In Pubmed:

(((peer support OR peer education OR peer group OR peer coach OR community worker OR (self-management AND (peer support OR peer education OR peer group OR peer coach OR community worker))) AND ((diabetes AND Type 2) OR T2DM)))

In ScienceDirect:

(tak(peer support) or tak(peer group) or tak(peer education) or tak(peer coach) or tak(community worker))AND ((tak(diabetes) AND tak(type 2)) or tak(T2DM))

In Web of Science:

(TS=(((peer support OR peer education OR peer group OR peer coach OR community worker OR (self-management AND (peer support OR peer education OR peer group OR peer coach OR community worker))) AND ((diabetes AND Type 2) OR T2DM))))

Supplementary Table S1 Characteristics of intervention group and control group

Study	Intervention group	Control group
Thom, D. H., 2013 [18]	**Provider: Peer coaches** Coaches were individuals with controlled diabetes, HbAc1<8.5% **IG:** Patients were paired with a coach based on their preference. Coaches interacted with patients assigned to them either in person, by telephone, or during a clinic visit Target goals for coaching sessions were telephone contact **at least twice a month and 2 or more in-person contacts over 6 months**.	**CG:** Patients in control group accepted usual care
Murrock, C. J., 2009 [27]	**Provider: Peer support group** **IG:** The dance intervention was taught by an experienced African American woman dance instructor, who led each dance class **2 evenings a week for 12 weeks, for a total of 24 classes**. During the first week of the dance classes, each woman chose a personal goal for improving 1 diabetes outcome and shared it with the group. After each class, the women had the opportunity to share their progress of working toward their goals, share tips for eating at upcoming weddings and family reunions, and discuss other concerns related to living with diabetes.	**CG:** The women randomized to the usual care group continued with their normal daily routines, medication schedule, diet, and glucose-monitoring regimen.
Lorig, K., 2009 [28]	**Provider: Peer leaders (N=18)** Most had type 2 diabetes and were not health professionals. They received 4 days of training. **IG:** Patients in IG received DSMP intervention. Program content included all areas of the American Association of Diabetes Education Standards (AADES7) with two exceptions. The program is highly interactive with emphasis on action planning and problem solving.	**CG:** Patients in control group accepted usual care
Lujan, J., 2007 [32]	**Provider: *Promotoras*** The *promotoras* were bilingual clinic employees who had received 60 hours of training on diabetes self-management **IG:** A team of 2 *promotoras* delivered **8 weekly, 2-hour,** participative group classes and telephone follow-up to the intervention participants.	**CG:** Patients received the usual one-on-one patient education by the clinic staff during scheduled medical follow-up visits, which consisted of verbal information and 1 or 2 pamphlets on diabetes self-management skills.
Duggan, C., 2014 [16]	**Provider: Community health workers (CHWs)** CHWs were trained in both diabetes education and in working with the community **IG:** The intervention consisted of **5 guided educational sessions** conducted in participants' homes. At each session, the CHW presented an educational curriculum involving diabetes education and awareness and methods to increase self-management of diabetes.	**CG:** Patients in control group accepted usual care

Cade, J. E., 2009 [30]	**Provider: Peer educators** Peer educators were people with diabetes, living in the community, who were willing to be trained in chronic disease self-management and to deliver group sessions on chronic disease self-management to other people with diabetes **IG:** A diabetes-specific EPP Subjects attended a **2-h session, once a week, for 7 weeks**.	**CG:** Individual one-off appointments with a dietitian (15-30 min)
Gagliardino, J. J., 2013 [20]	**Provider: Peer supporter** Peers received 3-day training and delivered four module patient education courses for the peer group **IG:** **4-week structured diabetes education course** delivered by previously trained peers Received regular peer cellular **phone calls (at least weekly for the first 6 months, biweekly for the next 3 months and monthly for the remaining study period**) and **bimonthly face-to-face interviews** in small groups (ten patients)	**CG:** 4-week structured diabetes education course delivered by professional educator
Lorig, K., 2008 [31]	**Provider: Peer leaders** Spanish-speaking peer leaders (N=43) who received 4 days of training came from the same communities as the participants. Most had type 2 diabetes and were not health professionals. **IG:** The SDSMP is a **6-week program offered 2.5 h weekly** by two peer leaders. **Automated telephone reinforcement monthly**	**CG:** Patients in control group accepted usual care
Smith, S. M., 2011 [23]	**Provider: Peer supporters** Peer supporters had type 2 diabetes for at least one year, had good adherence in practices and capability, and received peer support training. **IG:** The peer support intervention ran **over a two year period with nine group meetings** led by peer supporters in participant's own general practice (**at month one, month two, and every three months thereafter**) and a retention plan for the peer supporters.	**CG:** Patients in control group accepted usual care
Philis-Tsimikas, A., 2011 [24]	**Provider: Peer educator or *promotora*** Individuals with diabetes who exemplified the traits of a natural leader were identified from the patient population and trained as *promotoras* over a 3-month period **IG:** **Eight weekly, 2-h diabetes self-management classes and subsequent monthly support groups,** led by a trained peer educator	**CG:** Patients in control group accepted usual care
Dale, J., 2009 [29]	**Provider: Peer supporters** 9 peer supporters (6 had type 2 diabetes) received a 2-day training programme developed for the study. **IG:** Telecare support was intended to supplement routine care by motivating adherence to the advice provided peer supporters. **The first telecare call was made 3–5 days later, and the 'standard**	**CG:** Received a single call from a researcher at day 3–5

	package' offered subsequent contact at the following points: days 7–10, 14–18, 28–35, 56–70, 120–150.	
Prezio, E. A., 2013 [19]	**Provider: CHW** Bilingual female CHW received 27h training. **IG:** Per protocol, subjects in the intervention group received **7h of contact with the CHW during scheduled appointments over 12 months** in a private dedicated office space.	**CG:** Patients in control group accepted usual care
Perez-Escamilla, R., 2014 [18]	**Provider: CHWs** Well-trained and supervised bilingual/bicultural CHWs **IG:** The CHWs visited the treatment group participants at home **weekly during the first month, biweekly during months 2 and 3, and monthly thereafter until month 12**. At each visit, the CHW and patient jointly developed a T2MD self-management plan based on the individual patient's clinical history and previous challenges experienced with T2MD self-management.	**CG:** Patients in control group accepted usual care
Baghiani moghadam, M. H., 2012 [22]	**Provider: Peer educators** In Peer education group 2 patients that have the best scores in first questionnaire evaluations were chosen as educator and then received training. **IG:** IG was divided into two 20 patients groups. Peer educator was presented in two sessions and educates his audience with presentation, film and group conversation.	**CG:** Patients in CG had been educated by the researcher in the same manner.
Rothschild, S. K., 2014 [14]	**Provider: CHWs** 10 CHWs received more than 100 hours of training **IG:** CHWs delivered behavioral self-management training during **36 home visits over 2 years**.	**CG:** 36 mailed newsletters covered the AADE 7 topics and the 5 general self-management skills, providing control participants with the same number of contacts as received by those in the intervention arm and comparable diabetes self-management education
Ruggiero, L., 2010 [25]	**Provider:** A certified medical assistant with specific training in diabetes self-care and behavioral coaching **IG:** Guided by behavioral theory; 6-month period; patient-centered; sessions were designed to be brief (**<30 minutes for face-to-face clinic contacts, <15 minutes for telephone contacts**) and involved **two sessions during quarterly clinic visits (baseline, 3 months) and 4 monthly telephone calls between visits (months 1, 2, 4, 5)**.	**CG:** Patients in control group accepted usual care

Long, J. A., 2012 [21]	**Provider: Peer mentor** Peer mentors were all African American patients whose glucose control had previously been poor but was currently good **IG:** Peer mentors help patients identify the differences between his or her behaviors and goals, and help identify a realistic plan for goal achievement. Calls were not monitored. No face-to-face meetings between mentors and mentees were required—mentors were given the telephone number of their mentees and informed that they would receive $20 per month if the mentees confirmed that they talked **at least once per week**.	**CG:** Patients in control group accepted usual care.
Tang, T. S., 2014 [13]	**Provider: Peer leaders** The PLs were volunteers and received only a modest stipend to defray costs of participation **IG:** **A 6-month DSME program followed by 12 months of weekly group sessions** delivered by peer leaders with telephone outreach to those unable to attend	**Provider: CHWs** The CHWs had an average of 6 years' experience leading DSME at CHASS. They were all employees of the health clinic and received a salary **CG:** A 6-month DSME program followed by 12 months of monthly telephone outreach delivered by CHWs. The primary outcome was HbA1c
Chan, J. C. N., 2014 [17]	**Joint Asia Diabetes Evaluation (JADE)+Peer Support Empowerment and Remote Communication Linked by Information Technology (PEARL)** **Provider: Peer supporters** 33 motivated patients with well-controlled T2DM received 32 hours of training (four 8-hour workshops) to become peer supporters, with 10 patients assigned to each **IG:** Peer supporters called their peers at least 12 times, guided by a checklist	**CG:** Only JADE and usual care
Heisler, M., 2010 [26]	**Provider: Peer partners** **IG:** RPS participants attended a **3-hour group session and peer partners were encouraged to call each other at least once a week** using an interactive voice response-facilitated telephone platform. Participants were also **offered three optional 1.5 hour group sessions at months 1, 3, and 6**	**CG:** Participants in both arms attended an initial session led by a nurse care manager to review and discuss their point-of-service HbA1c and blood pressure values, and most recent medical record cholesterol values

CG, control group; IG, intervention group

Supplementary Table S2 Risk of bias

Study	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	other
Thom, D. H., 2013 [18]	Low risk	Low risk	High risk	Low risk	Unclear risk	Low risk
Murrock, C. J., 2009 [27]	Low risk	Low risk	High risk	Low risk	Unclear risk	Low risk
Lorig, K., 2009 [28]	Low risk	Unclear risk	High risk	Low risk	Unclear risk	Low risk
Lujan, J., 2007 [32]	Unclear risk	Unclear risk	High risk	Low risk	Unclear risk	Low risk
Duggan, C., 2014 [16]	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk
Cade, J. E., 2009 [30]	Unclear risk	Unclear risk	High risk	Low risk	Unclear risk	Low risk
Gagliardino, J. J., 2013 [20]	Unclear risk	Unclear risk	High risk	Low risk	Unclear risk	Low risk
Lorig, K., 2008 [31]	Unclear risk	Unclear risk	High risk	Low risk	Unclear risk	Low risk
Smith, S. M., 2011 [23]	Low risk	Unclear risk	High risk	Low risk	Unclear risk	Low risk
Philis-Tsimikas, A., 2011 [24]	Low risk	Unclear risk	High risk	Low risk	Unclear risk	Low risk
Dale, J., 2009 [29]	Low risk	Unclear risk	High risk	Low risk	Unclear risk	Low risk
Prezio, E. A., 2013 [19]	Unclear risk	Unclear risk	High risk	Low risk	Unclear risk	Low risk
Perez-Escamilla, R., 2014 [18]	Low risk	Low risk	High risk	Low risk	Unclear risk	Low risk
Baghianimoghadam, M. H., 2012 [22]	Unclear risk	Unclear risk	High risk	Low risk	Unclear risk	Low risk
Rothschild, S. K., 2014 [14]	Low risk	Unclear risk	High risk	Low risk	Unclear risk	Low risk
Ruggiero, L., 2010 [25]	Unclear risk	Unclear risk	High risk	Low risk	Unclear risk	Low risk
Long, J. A., 2012 [21]	Low risk	Unclear risk	High risk	Low risk	Unclear risk	Low risk
Tang, T. S., 2014 [13]	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk
Chan, J. C. N., 2014 [17]	Low risk	Low risk	High risk	Low risk	Unclear risk	Low risk
Heisler, M., 2010 [26]	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk

Supplementary Table S3 GRADE results

peer support for type 2 diabetes			
Bibliography: The Glycemic Control Effect of Peer Support for Adults with Type 2 Diabetes: A Meta-analysis on Randomized Clinical Trials			
Outcomes	**No of Participants (studies)** Follow up	**Quality of the evidence** (GRADE)	**Anticipated absolute effects** **Risk difference with Peer support** (95% CI)
Overall results of peer support intervention effect	3946 (20 studies)	⨁⨁⨁⨀ **MODERATE**[1] due to imprecision	The mean overall results of peer support intervention effect in the intervention groups was **0.16 lower** (0.25 to 0.007 lower)
Effect of interventions no more than 3 months	926 (5 studies)	⨁⨁⨁⨀ **MODERATE**[2] due to imprecision	The mean effect of interventions no more than 3 months in the intervention groups was **0.01 lower** (0.16 lower to 0.15 higher)
Effect of interventions more than 3 months but no more than 6 months	1468 (9 studies)	⨁⨁⨁⨀ **MODERATE**[3] due to imprecision	The mean effect of interventions more than 3 months but no more than 6 months in the intervention groups was **0.28 lower** (0 higher to 0.09 lower)
Effect of intervention no less than 12 months	1552 (6 studies)	⨁⨁⨁⨁ **HIGH**	The mean effect of intervention no less than 12 months in the intervention groups was **0.21 lower** (0.34 to 0.07 lower)
Effect of intervention provided by peer leaders (PLI)	2755 (12 studies)	⨁⨁⨁⨀ **MODERATE**[4] due to imprecision	The mean effect of intervention provided by peer leaders (pli) in the intervention groups was **0.08 lower** (0.18 to 0.03 lower)
Effect of intervention provided by peer partners (PPI)	254 (2 studies)	⨁⨁⨀⨀ **LOW**[5] due to risk of bias	The mean effect of intervention provided by peer partners (ppi) in the intervention groups was **0.49 lower** (0.86 to 0.12 lower)
Effect of intervention provided by community health workers (CHWI)	937 (6 studies)	⨁⨁⨁⨁ **HIGH**[6]	The mean effect of intervention provided by community health workers (chwi) in the intervention groups was **0.35 lower** (0 higher to 0.16 lower)
Effect of TDI	1062 (4 studies)	⨁⨁⨁⨁ **HIGH**[7]	The mean effect of tdi in the intervention groups was **0.12 lower** (0.31 lower to 0.07 higher)
Effect of SGI	609 (4 studies)	⨁⨁⨁⨁ **HIGH**	The mean effect of sgi in the intervention groups was **0.13 lower** (0.29 lower to 0.04 higher)
Effect of COI	488 (2 studies)	⨁⨁⨀⨀ **LOW**[5,8] due to risk of bias, imprecision	The mean effect of coi in the intervention groups was **0.01 higher** (0.23 lower to 0.25 higher)
Effect of CCRI	1189 (7 studies)	⨁⨁⨁⨀ **MODERATE**[9] due to imprecision	The mean effect of ccri in the intervention groups was **0.24 lower** (0.43 to 0.06 lower)
Effect of HVI	598 (3 studies)	⨁⨁⨁⨀ **MODERATE**[5,6] due to risk of bias	The mean effect of hvi in the intervention groups was

			0.3 lower (0.53 to 0.07 lower)
Follow-up during the intervention	495 (3 studies)	⊕⊕⊕⊖ **MODERATE**[10] due to risk of bias	The mean follow-up during the intervention in the intervention groups was **0.37 lower** (0.59 to 0.15 lower)
Follow-up immidiately after the intervention	3138 (17 studies)	⊕⊕⊕⊖ **MODERATE**[3] due to imprecision	The mean follow-up immidiately after the intervention in the intervention groups was **0.21 lower** (0.31 to 0.11 lower)
Follow-up 1-6 months after the end of intervention	1012 (5 studies)	⊕⊕⊕⊕ **HIGH**[11]	The mean follow-up 1-6 months after the end of intervention in the intervention groups was **0.06 lower** (0.26 lower to 0.15 higher)
Follow-up>6 months after the end of intervention	290 (2 studies)	⊕⊕⊖⊖ **LOW**[5,12] due to risk of bias, imprecision	The mean follow-up>6 months after the end of intervention in the intervention groups was **0.01 higher** (0.32 lower to 0.34 higher)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Four studies [13; 21; 28; 31] did not provide sd of mean of HbA1c after intervention, so we used the corresponding sd values at baseline. In 17 studies [13-15; 17-27; 29; 31; 32], we used the HbA1c results of 0 month follow-up to represent the effect of intervention. However, 3 studies [16; 28; 30] only provided the results of 1.75-month follow-up, 4.5-month follow-up and 10.25 follow-up respectively. Therefore, for these 3 studies, we used the corresponding results of each study to represent the effect of intervention.
[2] One studies [28] did not provide sd of mean of HbA1c after intervention, so we used the corresponding sd values at baseline.3 studies [16; 28; 30] only provided the results of 1.75-month follow-up, 4.5-month follow-up and 10.25 follow-up respectively. Therefore, for these 3 studies, we used the corresponding results of each study to represent the effect of intervention.
[3] Three studies [13; 21; 31] did not provide sd of mean of HbA1c after intervention, so we used the corresponding sd values at baseline.
[4] Four studies [13; 21; 28; 31] did not provide sd of mean of HbA1c after intervention, so we used the corresponding sd values at baseline. Two studies [28; 30] only provided the results of4.5-month follow-up and 10.25 follow-up respectively. Therefore, for these 2 studies, we used the corresponding results of each study to represent the effect of intervention.
[5] The number of studies in this group is limited.
[6] One study [16] only provided the results of 1.75-month.Therefore, we used the corresponding results of this study to represent the effect of intervention.
[7] One studies [21] did not provide sd of mean of HbA1c after intervention, so we used the corresponding sd values at baseline.
[8] All studies [28; 30] in this subgroup only provided the results of4.5-month follow-up and 10.25 follow-up respectively. Therefore, for these 2 studies, we used the corresponding results of each study to represent the effect of intervention.
[9] Two studies [13; 31] did not provide sd of mean of HbA1c after intervention, so we used the corresponding sd values at baseline.
[10] Results of two follow-up intervals came from the same study [15].
[11] One studies [13] did not provide sd of mean of HbA1c after intervention, so we used the corresponding sd values at baseline
[12] There are only two studies in this subgroup and one studies(13) did not provide sd of mean of HbA1c after intervention. We used the corresponding sd values of this study [13] at baseline

Sensitivity Analysis

According to the results in Supplementary Figure 1, the sensitivity of the 20 studies was low as the value and CI of each result were minus.

Study ommited	Coef.	[95% Conf.	Interval]
Thom, D. H.,2013	-.19449668	-.3293964	-.05959694
Murrock, C. J., 2009	-.20387521	-.33996573	-.0677847
Lorig, K., 2009	-.22802067	-.36878437	-.08725698
Lujan, J., 2007	-.21008015	-.34855628	-.071604
Duggan, C., 2014	-.23125379	-.36969537	-.09281223
Cade, J. E., 2009	-.22589345	-.36675951	-.08502739
Gagliardino, J. J., 2013	-.2136021	-.35636729	-.07083692
Lorig, K., 2008	-.20646374	-.34682387	-.06610361
Smith, S. M., 2011	-.23046528	-.37317201	-.08775854
Philis-Tsimikas, A., 2011	-.21532817	-.3537651	-.07689125
Dale, J., 2009	-.22840998	-.36647654	-.09034339
Prezio, E. A., 2013	-.17976639	-.30893174	-.05060104
Perez-Escamilla, R., 2014	-.19282708	-.32747617	-.058178
Baghianimoghadam, M. H., 2012	-.22683498	-.37041369	-.08325628
Rothschild, S. K., 2014	-.17283784	-.299346	-.04632969
Ruggiero, L., 2010	-.21536604	-.35095564	-.07977644
Long, J. A., 2012	-.18017094	-.30417073	-.05617112
Tang, T. S., 2014	-.2201114	-.3560757	-.08414709
Chan, J. C. N., 2014	-.22987033	-.37304226	-.08669842
Heisler, M., 2010	-.19286832	-.3289054	-.05683123
Combined	-.20976864	-.34329054	-.07624675

Supplementary Figure 1 Sensitivity Analysis Results

Publication Bias

According to Supplementary Figure 2, we found a little publication bias because of $P = 0.045$. Therefore, we performed Trim and fill method (Supplementary Figure 3) to test the bias again, and the results showed that the results were steady and there was no publication bias. Combined the two results of publication bias, we got a conclusion that although there was a little publication bias among our 20 studies, the bias was not serious and could be accepted.

```
Tests for Publication Bias

Begg's Test

  adj. Kendall's Score (P-Q) =      -56
        Std. Dev. of Score =    30.82
         Number of Studies =       20
                         z  =    -1.82
                  Pr > |z| =    0.069
                         z  =     1.78 (continuity corrected)
                  Pr > |z| =    0.074 (continuity corrected)

Egger's test
------------------------------------------------------------------------------
     Std_Eff |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       slope |   .1655662   .1614642     1.03   0.319    -.1736575    .5047899
        bias |  -1.726387   .8018188    -2.15   0.045    -3.410946   -.0418281
------------------------------------------------------------------------------
```

Supplementary Figure 2 Egger's and Begg's Test

```
Meta-analysis

       |  Pooled      95% CI         Asymptotic      No. of
Method |     Est   Lower   Upper  z_value  p_value   studies
-------+-----------------------------------------------------
Fixed  |  -0.159  -0.247  -0.071   -3.527    0.000     20
Random |  -0.210  -0.343  -0.076   -3.079    0.002

Test for heterogeneity: Q= 37.649 on 19 degrees of freedom (p= 0.007)
Moment-based estimate of between studies variance =  0.041

Trimming estimator: Linear
Meta-analysis type: Random-effects model

iteration |  estimate    Tn    # to trim     diff
----------+-----------------------------------------
    1     |   -0.210     98         0         210
    2     |   -0.210     98         0           0

Note: no trimming performed; data unchanged

Filled
Meta-analysis

       |  Pooled      95% CI         Asymptotic      No. of
Method |     Est   Lower   Upper  z_value  p_value   studies
-------+-----------------------------------------------------
Fixed  |  -0.159  -0.247  -0.071   -3.527    0.000     20
Random |  -0.210  -0.343  -0.076   -3.079    0.002

Test for heterogeneity: Q= 37.649 on 19 degrees of freedom (p= 0.007)
Moment-based estimate of between studies variance =  0.041
```

Supplementary Figure 3 Trim and fill method

7

Chapter 7

How to perform better intervention to prevent and control diabetic retinopathy among patients with type 2 diabetes: A meta-analysis of randomized controlled trials

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Xinying Sun, Hein Raat, Ningli Wang

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DIABETES RESEARCH AND CLINICAL PRACTICE 2019;156:107834

ABSTRACT

This meta-analysis of randomized controlled trials (RCTs) aims to investigate how to perform better interventions targeting modifiable risk factors of diabetic retinopathy (DR) to prevent and control DR in patients with type 2 diabetes by comparing different intervention types and follow-up intervals. Literature published before June 1st, 2019 were searched on Pubmed, Embase and ScienceDirect. RCTs targeting modifiable risk factors of DR (including blood glucose, blood pressure, lipid, dietary, physical activity and smoking) were selected by two reviewers and double checked for accuracy. Random effects models were estimated to calculate pooled Odds Ratios (OR). Twenty-two RCTs (n = 22511) were included. In general, interventions targeting modifiable risk factor of DR reduced the risk of developing DR (I^2 = 26.7%; OR = 0.60; 95% CI 0.45 to 0.79; P < 0.001) and DR worsening (I^2 = 0%; OR = 0.62; 95% CI 0.47 to 0.80; P < 0.001). Multifactorial interventions had better effect on reducing the risk of development and progression of DR in comparison with other interventions, while only blood-pressure-control interventions showed significant effect on slowing down DR worsening. Additionally, interventions with follow-up >5 years had better effect on reduction of DR development, and interventions with follow-up >2 years had better effect on reducing the risk of DR worsening.

KEYWORDS Diabetic retinopathy; Type 2 diabetes; Prevention; Multifactorial intervention; Meta-analysis

INTRODUCTION

Diabetic retinopathy (DR), a microvascular complication of diabetes, is the leading cause of preventable blindness in working age population.[1, 2] It is reported that after 20 years, nearly all patients with type 1 diabetes and more than 60% of those with type 2 diabetes will develop DR.[3]

Studies have identified risk factors of DR development and progression, such as duration of diabetes, hyperglycemia/glycated hemoglobin value (HbA1c), hypertension, hyperlipidemia, pregnancy, nephropathy/renal disease, obesity, smoking, moderate alcohol consumption and physical activity.[1, 3]

Several intervention studies aiming at identifying the effect of intervention targeting modifiable risk factors of DR among patients with type 2 diabetes have been conducted. However, the results of these trials are not consistent in terms of the effect of interventions on reducing the risk of developing DR and/or its worsening. For instance, with regard to the interventions on hyperglycemia, the Veterans Affairs Diabetes Trial (VADT) found intensive glucose control had no significant effect on preventing DR development but had significant effect on slowing down its worsening[4, 5], while the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial found that intensive glucose control had no effect on delaying DR progression (development or worsening).[6] In the meantime, another study conducted in Japan found that intensive glucose control had significant effect on reducing the risk of both development and worsening of DR.[7] With respect to interventions on hypertension, the Appropriate Blood Pressure Control in Diabetes (ABCD) trail[8] found intensive blood pressure control had no effect on preventing DR development, but UK Prospective Diabetes Study (UKPDS)[9, 10] found it to be significantly effective. In addition, some trails have also proven that interventions on multi-factors like blood glucose, blood pressure, dietary, physical activity and smoking were effective.[11-13] To date, no study has gathered all the evidence on different kinds of interventions targeting modifiable risk factors of DR and compared their effects to find out how to better perform interventions to prevent and control DR among patients with type 2 diabetes.

This study aims to answer the following three questions by carrying out a meta-analysis of randomized control trials (RCTs):

First, could interventions targeting modifiable risk factors of DR (blood glucose, blood pressure, lipid, dietary, physical activity and smoking) reduce the risk of developing DR and/or its worsening among patient with type 2 diabetes?

Second, among these interventions, what type of intervention is most effective in reducing the risk of developing DR and/or its worsening?

Third, how long should follow-up interval of interventions be to better reduce the risk of developing DR and/or its worsening?

MATERIALS AND METHODS

Data sources and searches

Pubmed, Embase and ScienceDirect were searched with terms related to our study aim, including "prevention", "intervention", "glycemic control", "HbA1c", "blood pressure control", "lipids", "diet", "physical activity", "smoking", "diabetic retinopathy", "DR", "type 2 diabetes", "T2DM" and other synonyms to identify articles related to our study from January 1st, 1980 to June 1st, 2019. PubMed was searched with MeSH terms and other synonyms in title/abstract/keywords and identified 503 articles. Embase was searched with Emtree terms and other synonyms in title/abstract/keywords and identified 1008 articles. ScienceDirect was searched with keywords in title/abstract/keywords of research articles and identified 885 articles. After excluding duplicates, a total of 1991 articles were identified, and details of the search syntax can be found in the Supplementary Data.

Study selection

Eligible studies were screened from the 1991 articles based on the inclusion and exclusion criteria below.

Inclusion criteria:

1. Studies with a randomized-controlled design presenting original research
2. Study participants: patients with type 2 diabetes (If the type of diabetes was unclear, the study was included if the mean age of patients was over 30 because most of these patients were likely to have type 2 diabetes.)
3. Studies that aimed to study the effect of interventions targeting modifiable risk factors of DR (including blood glucose, blood pressure, lipid, dietary, physical activity and smoking) on the prevention and control of DR
4. Studies that provided data that could be used to calculate Odds Ratio (OR) in order to evaluate the effect of interventions targeting modifiable risk factors of DR on the prevention and control of DR (e.g. The number of patients who developed or did not develop DR in both intervention group (IG) and control group (CG); the number of DR patients whose condition worsened or did not worsen in both groups; or other related data from which the useful data could be derived)

Exclusion criteria:

1. Study participants: Patients under 18 years old
2. The intervention is medical treatment of DR rather than just targeting modifiable risk factors of DR (e.g. drugs, medical examinations, and surgeries)
3. Non-English publications

Of the 1991 articles, on the basis of the study titles and abstracts, two reviewers (Yusufu and Zhang) excluded 1903 articles that: were not RCTs; were not original research (e.g. reviews, secondhand-data analysis, and design studies); studied type 1 diabetes, gestational diabetes or other specific types of diabetes; studied patients under 18 years old; did not study the effect of interventions targeting modifiable risk factors of DR on the prevention and/or control of DR, adopted medical treatment of DR as interventions (e.g. drugs or medicines, medical examinations, or surgeries); or were not published in English. Two reviewers (Yusufu and Zhang) independently examined the full-text of the remaining 88 articles. Among those, 72 were excluded mainly due to lack of basic data that would be needed to evaluate the effect of intervention on the prevention and control of DR (Figure 1). In case of disagreement, the reviewers discussed with a third researcher (Sun) to reach an agreement and all disagreements were resolved by consensus. Finally, 16 articles[5-8, 10-21] on 22 studies were included in this meta-analysis.

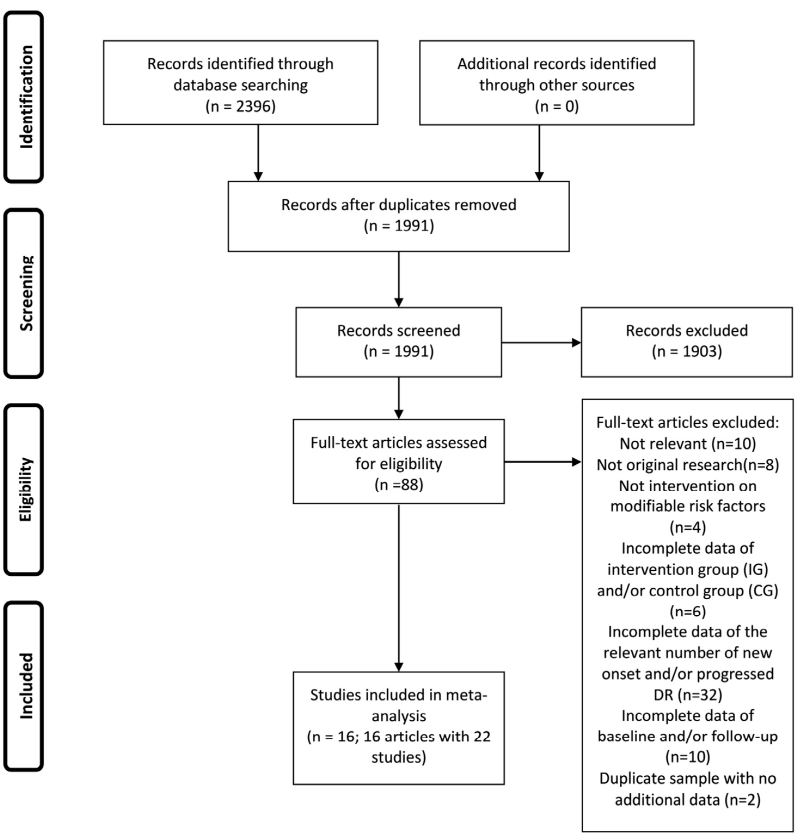

Figure 1 Flowchart of study selection

Data extraction and quality assessment

Data from the 22 studies were extracted by two reviewers (Yusufu and Zhang) with a standardized data extraction form. The extraction form included: the name of the study (most studies had an official name; if not, the study was named after the first author), the year of publication, number of participants, follow-up interval, the characteristics of participants (including data of IG and CG respectively, e.g. types of patients, gender ratio, mean age, duration of diabetes, glycated hemoglobin, blood pressure, total cholesterol, body mass index and percentage of patients without DR at baseline), study design and location, intervention methods, the number of participants who developed or did not develop DR in both IG and CG, and/or the number of DR patients whose condition worsened or did not worsen in both groups, and/ or the number of participants with DR progression (For studies failing to provide distinctive data on new onset and worsening DR, the term "progression" was adopted to cover both new onset and worsening DR). The details of each study can be found in Supplementary Table S1 and S2.

In all 22 studies, ophthalmologists diagnosed and/or evaluated DR based on on-site ophthalmoscopy or report from the primary care physicians. Most studies[5-8, 10, 14, 18, 19, 21] adopted the protocol of the Early Treatment Diabetic Retinopathy Study (ETDRS) to define the grade of DR and make diagnosis of DR. Some studies adopted the Wisconsin Epidemiologic Study of Diabetic Retinopathy[15, 17], the EURODIAB six-level grading[11, 12, 16], and other grading scales[13, 20] to define the grade of DR and make diagnosis of DR. DR worsening was defined as a change of at least two steps from baseline measurement in any eye.[5, 7, 8, 10, 14] One study[11] defined DR worsening based on an increase of at least one level in any eye. DR progression was defined as a change of at least two or three steps from baseline measurement in any eye.[6, 18, 19, 21] Two studies[12, 16] defined DR progression as an increase of at least one level in any eye. The detailed criteria used for the diagnosis, worsening and progression of DR in each study can be found in Supplementary Table S3.

Some studies did not provide the needed data, in which case, the data needed for the evaluation of the effect of interventions were obtained through calculation. One study[8] only provided the percentage of patients who developed DR at follow-up in the IG and CG respectively. We calculated the number of patients with newly developed DR based on the percentage and the number of patients. One study[15] provided the number of patients without DR at baseline and follow-up respectively in both IG and CG. We subtracted the number of patients without DR at follow-up from the number of patients without DR at baseline to obtain the number of patients with newly developed DR. One study[13] provided the number of patients with DR at baseline and follow-up in both IG and CG. We subtracted the number of patients with DR at baseline from the number of patients with DR at follow-up to get the number of patients with newly developed DR.

The interventions were classified into five categories based on modifiable risk factors:1) Blood-pressure-control intervention, 2) Glycemic-control intervention, 3) Lipid-control

intervention, 4) Dietary-control intervention, and 5) Multifactorial intervention (interventions targeting more than one risk factors).

We applied the Cochrane Collaboration's tool to assess the risk of bias in our study. This tool consists of six domains: selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias. For each domain, the study was graded as having a low risk, high risk, or unclear risk of bias.[22] Grades of Recommendations Assessment, Development and Evaluation (GRADE) was used to evaluate the level of evidence in the meta-analysis with GRADEpro3.2. Two reviewers (Yusufu and Zhang) assessed each study independently. Disagreements between the reviewers were discussed with a third researcher (Sun) in order to reach an agreement.

Data synthesis and analysis

The heterogeneity between the studies was evaluated with the I^2 test. Random effects models were estimated to calculate pooled Odds Ratios (OR) of DR development, worsening and progression. For these analyses we considered a value of $P < 0.05$ to be significant. A sensitivity analysis was performed to test the stability of the studies by excluding one study at a time. Possible publication bias was assessed by estimating funnel plots with Begg and Egger tests, and a value of $P < 0.1$ was considered to be significant.[23, 24] We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist to report our meta-analysis study.[25] All statistical analyses were performed using Stata 11.0.

RESULTS

Study selection and Study Characteristics

The 22 studies included in this meta-analysis studied a total of 22,511 participants. The number of participants in each study ranged from 35[15] to 11,140[6]. In most studies, the number of males and females was similar[6-8, 10-13, 15-21], but in two studies[5, 14], over 90% of participants were male. The follow-up interval of the interventions ranged from 1 year[15] to 8 years[21]. Blood-pressure-control intervention was evaluated in 4 studies[8, 9, 19, 21], glycemic-control intervention was evaluated in 9 studies[5-7, 14, 15, 18, 19, 21]. Lipid-control intervention was evaluated in 2 studies[19, 21]. Dietary-control intervention was evaluated in 2 studies[20]. Multifactorial intervention was evaluated in 5 studies[11-13, 16, 17]. More details of the included studies can be found in Supplementary Table S1.

Risk of bias

None of the RCTs included in this review were double-blinded. In all studies, no high risk of bias was found in the domains of selection bias, detection bias, attrition bias, reporting bias, and other bias. More details of the risk of bias could be found in Supplementary Table S4.

Quality of the evidence for most results on new onset DR and DR worsening was moderate to high, except the results of glycemic-control intervention (new onset DR), glycemic-control intervention (DR Worsening), follow-up <2 years (DR Worsening) and follow-up >5 years (DR

Worsening) (The details are presented in Supplementary Table S5 and S6). Quality of the evidence for most results on DR progression was moderate to low (The details are presented in Supplementary Table S7), which was mainly caused by the substantial heterogeneity in this subgroup.

Results of intervention effects on DR prevention

A total of 11 studies from 10 articles[5, 7, 8, 10, 11, 13-15, 17, 20] provided data on the number of patients with newly developed DR. In one article[20], there were two intervention groups (Mediterranean diet supplemented with extra virgin olive oil group and Mediterranean diet supplemented with mixed nuts group) and one control group. Therefore, we divided this study into two studies by matching the control group with two intervention groups separately. Out of the 11 studies, 7 studies from 6 articles[7, 10, 11, 13, 17, 20] revealed a significant reduction in the number of newly developed DR in intervention group compared with control group, and 4 studies from 4 articles[5, 8, 14, 15] showed no effect.

Results on the effectiveness of all interventions targeting modifiable risk factors of DR in reducing the risk of developing DR among patients with type 2 diabetes are presented in Figure 2. Heterogeneity between studies was small (I^2 = 26.7%). The pooled results indicated that interventions targeting modifiable risk factor of DR reduced the risk of developing DR among patients with type 2 diabetes significantly (OR = 0.60; 95% CI 0.45 to 0.79; P < 0.001). The sensitivity of the 11 studies was low, and the Begg and Egger tests did not reveal publication bias. More details on the sensitivity analysis and publication bias assessment can be found in Supplementary Figure S1 and S2.

Results of subgroup analyses on the effectiveness of different types of interventions are presented in Figure 2, Part A. There was moderate heterogeneity among blood-pressure-control intervention studies (I^2 = 41.9%). Blood-pressure-control intervention had no significant effect on reducing the risk of developing DR (OR = 0.68; 95% CI 0.41 to 1.14; P = 0.143). There was moderate heterogeneity among glycemic-control intervention studies (I^2 = 38.2%). Glycemic-control intervention had no significant effect on reducing the risk of developing DR (OR = 0.70; 95% CI 0.31 to 1.57; P = 0.387). There was no heterogeneity between dietary-control intervention studies (I^2 = 0%). Dietary-control intervention reduced the risk of developing DR significantly (OR = 0.64; 95% CI 0.43 to 0.95; P = 0.025). There was no heterogeneity among multifactorial intervention studies (I^2 = 0%). Multifactorial intervention reduced the risk of developing DR significantly (OR = 0.27; 95% CI 0.14 to 0.53; P < 0.001).

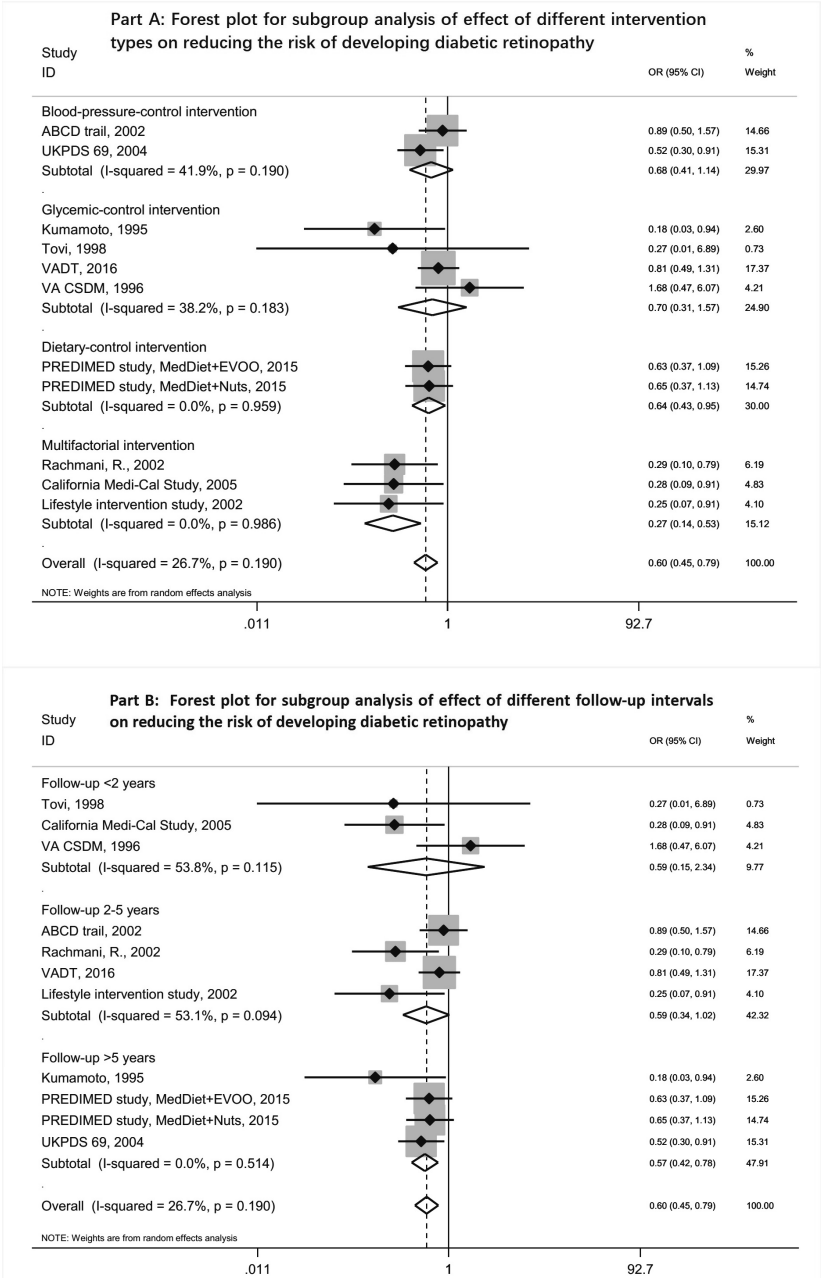

Figure 2 Forest plots for subgroup analysis on reducing the risk of developing diabetic retinopathy

Results of subgroup analyses on the effectiveness of different follow-up intervals are presented in Figure 2, Part B. There was substantial heterogeneity among interventions with follow-up <2 years (I^2 = 53.8%). Interventions with follow-up <2 years had no significant effect

on reducing the risk of developing DR (OR = 0.59; 95% CI 0.15 to 2.34; *P* = 0.452). There was substantial heterogeneity among interventions with follow-up of 2-5 years (I^2 = 53.1%). Interventions with follow-up of 2-5 years had no significant effect on reducing the risk of developing DR (OR = 0.59; 95% CI 0.34 to 1.02; *P* = 0.060). There was no heterogeneity among interventions with follow-up over 5 years (I^2 = 0%). Interventions with follow-up of over 5 years reduced the risk of developing DR significantly (OR = 0.57; 95% CI 0.42 to 0.78; *P* < 0.001).

Results of intervention effects on DR control

Effects on DR worsening

A total of 7 studies from 7 articles[5, 7, 8, 10, 11, 14, 15] provided data on the number of patients suffering worsening DR. Out of the 7 studies, 4 studies from 4 articles[5, 7, 10, 11] found a significant effect on slowing the worsening of DR in intervention group compared with control group, while the remaining 3 studies from 3 articles[8, 14, 15] showed no effect.

Results on the effectiveness of all interventions targeting modifiable risk factors of DR in reducing the risk of DR worsening among patients with type 2 diabetes are presented in Figure 3. The pooled results showed that interventions targeting modifiable risk factor of DR reduced the risk of DR worsening in patients with type 2 diabetes significantly (OR = 0.62; 95% CI 0.47 to 0.80; *P* < 0.001). No heterogeneity between studies (I^2 = 0%) was found . The sensitivity of the 7 studies was low, and the Begg and Egger tests did not reveal publication bias. More details of sensitivity analysis and publication bias assessment can be found in Supplementary Figure S3 and S4.

Results of subgroup analyses on the effectiveness of different types of interventions are presented in Figure 3, Part A. Blood-pressure-control intervention had significant effect on slowing down the worsening of DR (OR = 0.52; 95% CI 0.34 to 0.78; *P* = 0.002) and no heterogeneity among blood-pressure-control intervention studies was found (I^2 = 0.0%). Glycemic-control intervention reduced the risk of DR worsening, but not significantly (OR = 0.71; 95% CI 0.50 to 1.00; *P* = 0.053), and no heterogeneity among glycemic-control intervention studies was found (I^2 = 0%). There is no pooled results of multifactorial intervention because there was only one study in this subgroup.

Results of subgroup analyses on different follow-up intervals are presented in Figure 3, Part B. Interventions with follow-up <2 years had no significant effect on reducing the risk of DR worsening (OR = 0.91; 95% CI 0.40 to 2.09; *P* = 0.826), and there was no heterogeneity (I^2 = 0%). Interventions with follow-up of 2-5 years reduced the risk of DR worsening significantly (OR = 0.68; 95% CI 0.49 to 0.94; *P* = 0.020), and there was no heterogeneity (I^2 = 0%). Interventions with follow-up of over 5 years had significant effect on reducing the risk of DR worsening (OR = 0.41; 95% CI 0.24 to 0.69; *P* = 0.001) and there was no heterogeneity (I^2 = 0%).

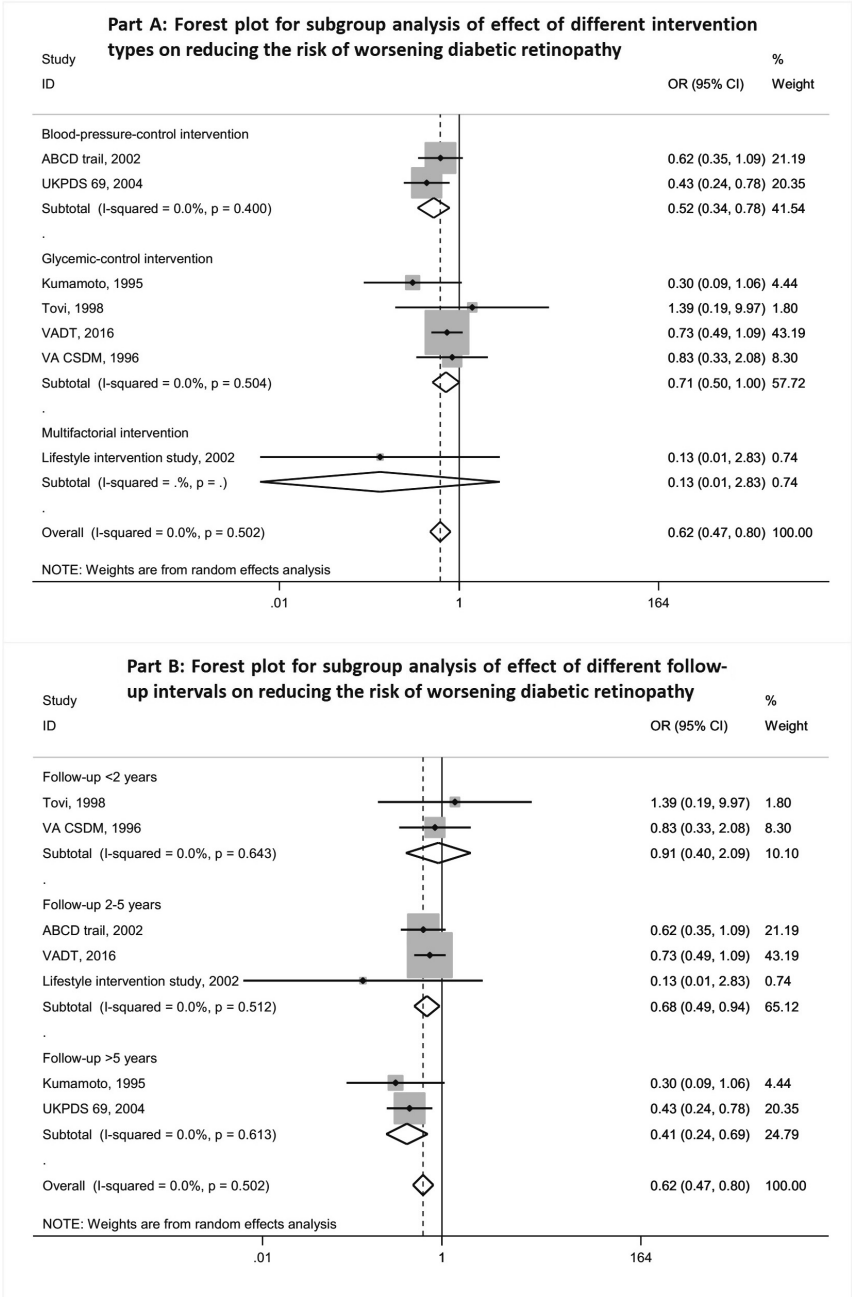

Figure 3 Forest plot for subgroup analysis on reducing the risk of worsening diabetic retinopathy

Effects on DR progression

A total of 10 studies from 6 articles[6, 12, 16, 18, 19, 21] provided data on the number of patients with DR progression. There are two articles [19, 21] each reporting the results on three studies. Out of the 10 studies, 5 studies from 4 articles[12, 16, 19, 21] found a significant reduction in the progression of DR in intervention group compared with control group, and 5 studies from 4 articles[6, 18, 19, 21] showed no effect.

Results on the effectiveness of all interventions targeting modifiable risk factors of DR in reducing the risk of DR progression among patients with type 2 diabetes are presented in Figure 4. The pooled results revealed that interventions targeting modifiable risk factor of DR reduced the risk of DR progression among patients with type 2 diabetes significantly (OR = 0.74; 95% CI 0.59 to 0.92; *P* = 0.007). The overall heterogeneity among studies was substantial (I^2 = 72.4%). The sensitivity of the 10 studies was low, and the Begg and Egger tests did not reveal publication bias. More details of sensitivity analysis and publication bias assessment can be found in Supplementary Figure S5 and S6.

Results of subgroup analyses on the effectiveness of different types of interventions are presented in Figure 4, Part A. Blood-pressure-control intervention had no effect on reducing the risk of DR progression (OR = 1.05; 95% CI 0.77 to 1.45; *P* = 0.749), and there was no heterogeneity (I^2 = 0%). Glycemic-control intervention reduced the risk of DR progression significantly (OR = 0.71; 95% CI 0.52 to 0.97; *P* = 0.032), and the heterogeneity was substantial (I^2 = 81.6%). Lipid-control intervention had no significant effect on reducing the risk of DR progression (OR = 0.83; 95% CI 0.44 to 1.59; *P* = 0.581), and the heterogeneity was substantial (I^2 = 79.5%). Multifactorial intervention reduced the risk of DR progression significantly (OR = 0.39; 95% CI 0.23 to 0.65; *P* <0.001), and there was no heterogeneity among multifactorial intervention studies (I^2 = 0%).

Results of subgroup analyses on different follow-up intervals are presented in Figure 4, Part B. There was substantial heterogeneity among interventions with follow-up of 2-5 years (I^2 = 66.4%). Interventions with follow-up of 2-5 years reduced the risk of DR progression significantly (OR = 0.73; 95% CI 0.59 to 0.91; *P* = 0.006). There was substantial heterogeneity among interventions with follow-up of over 5 years (I^2 = 85.9%). Interventions with follow-up of over 5 years had no significant effect on reducing the risk of DR progression (OR = 0.84; 95% CI 0.39 to 1.80; *P* = 0.648).

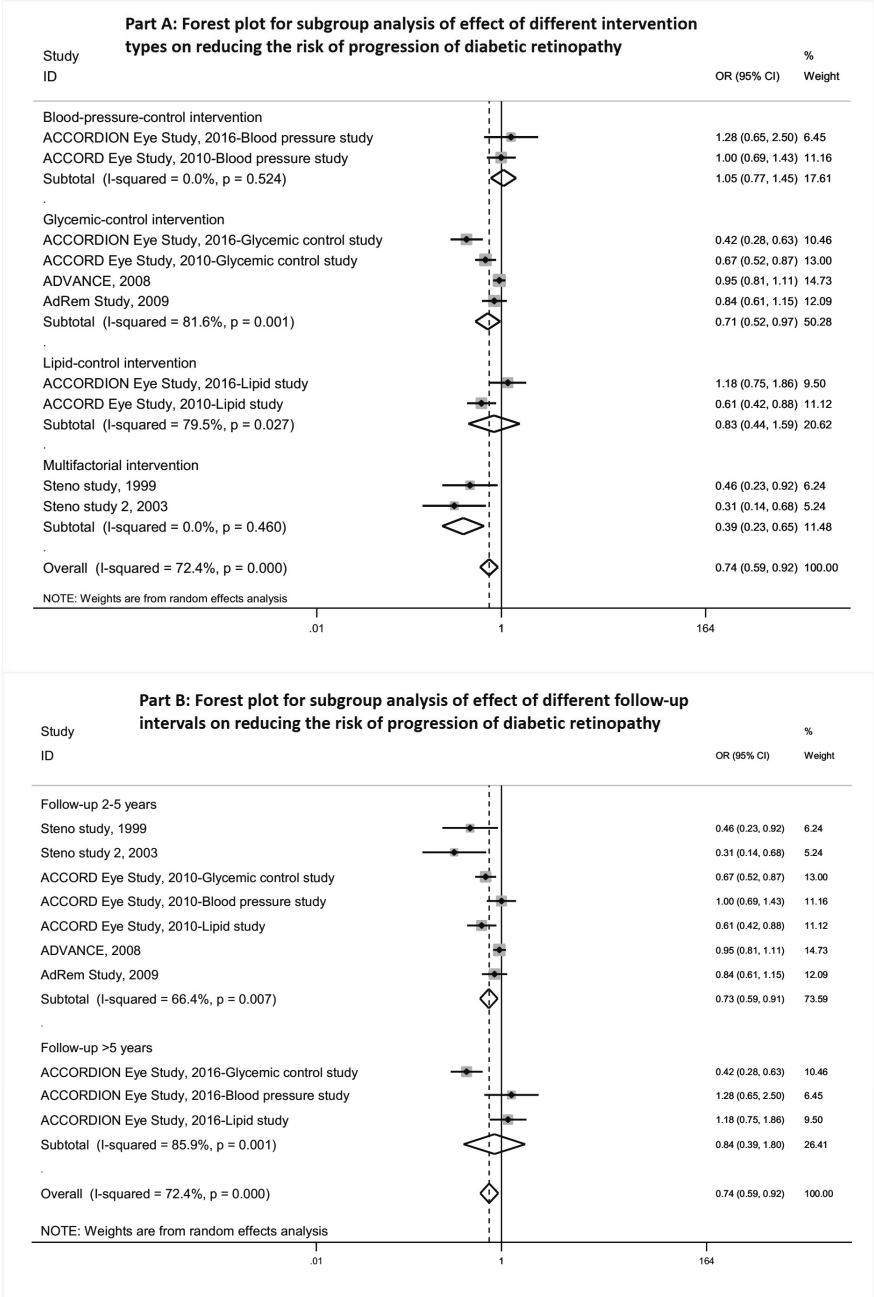

Figure 4 Forest plot for subgroup analysis on reducing the risk of progression of diabetic retinopathy

DISCUSSION

Our study found multifactorial intervention with individualized target and communication between health professionals and patients was more effective than other interventions in the prevention and control of DR. Interventions with follow-up of over 5 years had better effect on reduction of DR development, and interventions with follow-up of 2 to 5 years and over 5 years had better effect on reducing the risk of DR worsening.

Our study showed that the effect of multifactorial intervention on reducing the risk of DR development was superior to that of blood-pressure-control intervention, glycemic-control intervention or dietary-control intervention. A previous study on multifactorial intervention among patients with type 2 diabetes also found that "intensive intervention with multiple drug combinations and behavior modification had sustained beneficial effects with respect to vascular complications and on rates of death from any cause and from cardiovascular causes".[26] Apart from controlling multiple factors, we also found that the similarities of the multifactorial interventions on prevention of DR in the subgroup analysis were individualization and communication. Interventions and support for patients with type 2 diabetes were provided based on patients' situation.[11, 13, 17] For example, patients could get recommendations on individualized goals to reach and could attend age and gender-adjusted fitness programs.[13] Moreover, health professionals would communicate with patients through education sessions, phones and emails.[11, 13, 17]

Additionally, we found dietary-control intervention (Mediterranean diet supplemented with olive oil or nuts) are effective in preventing DR. A systematic review on dietary intake and diabetic retinopathy also found that Mediterranean diet, dietary fiber, fruits and vegetables, and oily-fish have protective effect on DR.[27] However, both studies in our subgroup analysis of dietary-control intervention are from the same article. The number of intervention studies exploring the effect of dietary intake on DR is very limited[20, 27], thus more longitudinal studies in this field are needed. According to our pooled results, controlling blood pressure or blood glucose alone had no significant effect on preventing DR among patients with type 2 diabetes. The finding on blood glucose control is consistent with results from a previous meta-analysis[1] on the effects of intensive glycemic control in ocular complications in patients with type 2 diabetes, which found no significant difference in the incidence of retinopathy. However, our finding on blood pressure is different from the result of a review of 15 RCTs on blood pressure stating that "the available evidence supports a beneficial effect of intervention to reduce blood pressure with respect to preventing diabetic retinopathy for up to 4 to 5 years".[28] The possible reason of the differences might be that in our study blood pressure control alone would be regarded as blood-pressure-control intervention, while in that review article, blood pressure control alone and blood pressure control in combination with other interventions were all classified as blood-pressure-control intervention. In addition, we only included studies on patients with type 2 diabetes but the review included patients with both type 1 and type 2 diabetes. Regarding to the follow-up intervals, our results showed that compared

with interventions with follow-up of 5 years or less, interventions with follow-up of over 5 years had better effect on preventing DR. A previous meta-analysis also had similar result that "more intensive glucose control over 5 years reduced both kidney and eye events" among patients with type 2 diabetes.[29]

Moreover, we explored the effect of interventions targeting modifiable risk factors of DR on its worsening specifically, which was rarely studied by previous meta-analysis studies. We found blood-pressure-control intervention was effective in slowing down DR worsening. However, controlling blood glucose alone had no significant effect on the control of DR worsening. A systematic review on DR also suggested that there is no evidence that rapid improvement of blood glucose control will reduce the risk of DR worsening.[30] As for follow-up intervals, our results showed that compared with interventions with follow-up of less than 2 years, interventions with follow-up of 2 to 5 years and over 5 years had better effect on reducing the risk of DR worsening. According to the analysis on the follow-up intervals, the effect of interventions on preventing DR can be observed after over 5 years, while the effect on slowing down DR worsening can be observed after 2 years, indicating that effect of interventions on delaying DR worsening could be observed earlier than that on preventing DR development.

Regarding DR progression (new onset or worsening), our results indicated that multifactorial intervention also had better effect on reduction of DR progression compared with the blood-pressure-control intervention, glycemic-control intervention and lipid-control intervention. Individualized methods were adopted in the multifactorial intervention to control the progression of DR.[11, 12, 16] For example, if patients could not reach the blood pressure goal and/or blood glucose goal set at the beginning after three months, stepwise approaches were adopted based on patients' situation.[12, 16] Additionally, we found glycemic-control intervention could reduce the risk of DR progression, which is consistent with previous meta-analysis.[1, 29] The control of blood pressure or lipid level alone had no significant effect on reduction of DR progression among type 2 diabetes according to our pooled results. A recent subgroup meta-analysis of 4 RCTs found a borderline significant reduction in DR progression with more intensive blood pressure lowering, which is different from our finding.[31] However, they did not focus on diabetic patients and also reported substantial heterogeneity of subgroup analysis. More studies on the effect of blood pressure control on DR would be needed. As for follow-up intervals, our results showed that compared with interventions with follow-up of over 5 years, interventions with follow-up of 2 to 5 years had better effect on reduction of DR progression. However, the heterogeneity among interventions with follow-up of over 5 years on DR progression was substantial. More studies are still needed to verify this finding.

Strengths and limitations

This meta-analysis is the first to report variation among different intervention types targeting modifiable risk factors of DR, and among different follow-up intervals of interventions in

patients with type 2 diabetes. However, the study still has several limitations. First, no RCT included in our meta-analysis was double-blinded study. Second, in subgroup analyses, the number of studies in some subgroups (blood-pressure-control intervention, dietary-control intervention and lipid-control intervention) were small and there was a high level of heterogeneity in some subgroups (the groups of glycemic-control intervention and follow-up of over 5 years for the analysis on effect on DR progression). One possible reason of heterogeneity might be studies included in the analyses of DR progression did not provide distinctive data for new onset and worsening DR, and the variation between studies might be large. Third, subgroup analyses on the influence of other factors (e.g. duration of diabetes, duration of DR, intervention duration and frequency) could not be conducted due to the limited number of studies. Fourth, our meta-analysis has not been registered online.

Implications for practice and future researches

We found that multifactorial interventions can significantly reduce the risk of developing DR and its progression among patients with type 2 diabetes. More importantly, we found all these multifactorial interventions contained individualization of targets and communication between health professionals and patients, suggesting ophthalmologists and diabetes health professionals should work together with patients to set more individualized targets while taking into account multiple factors so as to achieve optimal effect in DR prevention and control. Training on interventions on DR prevention and control should be carried out for general practitioners in primary level health facilities so that they can educate the patients with type 2 diabetes in this regard. In the future, guidelines on how to perform better and more effective DR prevention and control should be developed for general practitioners. In addition, more studies on the effectiveness of interventions targeting various modifiable risk factors of DR in prevention and control of DR are needed.

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Search Syntax:

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Supplementary Table S1 Characteristics of eligible studies included in meta-analysis

Study	Number of participants	Baseline characteristics of participants		Study design and Location	Intervention
		Intervention group	Control group		
ABCD trial, 2002	Baseline: Intervention group (IG): 237 Control group (CG): 243 Follow-up (5 years): IG: 195 CG: 202	Patients with type 2 diabetes Female (%): 47 Mean age: 58.5±0.6 Duration of diabetes (year): 8.8±0.5 Glycated hemoglobin (HbA1c) (%): 11.5±0.2 Blood pressure (mm Hg): Systolic: 135.6±0.8 Diastolic: 84.4±0.2 Total Cholesterol (mg/dl): LDL: - HDL: - BMI: 31.5±0.4 Without diabetic retinopathy (%): 50	Patients with type 2 diabetes Female (%): 44 Mean age: 59.6±0.5 Duration of diabetes (year): 9.2±0.5 HbA1c (%): 11.6±0.2 Blood pressure (mm Hg): Systolic: 137.2±0.9 Diastolic: 84.4±0.2 Total Cholesterol (mg/dl): LDL: - HDL: - BMI: 31.5±0.4 Without diabetic retinopathy (%): 50	RCT USA	**Blood-pressure-control intervention** Intensive (10 mmHg below the Baseline) control vs. Moderate (80 to 89mmHg) control
ACCORD Eye Study, 2010	**Glycemic control study** Baseline and Follow-up (4 years)* IG: 1429 CG: 1427	Patients with type 2 diabetes Female (%):37.6 Mean age: 61.6±6.4 Duration of diabetes (year): 9.8±7.1 HbA1c (%): 8.2±1.0 Blood pressure (mm Hg): Systolic: 134.3±16.6 Diastolic: 74.9±10.3 Total Cholesterol (mg/dl): LDL: 100.8±33.4 HDL: 42.0±11.4 BMI: 32.4±5.5 Without diabetic retinopathy (%): 51.1	Patients with type 2 diabetes Female (%): 38.7 Mean age: 61.5±6.3 Duration of diabetes (year): 10.1±7.2 HbA1c (%): 8.3±1.0 Blood pressure (mm Hg): Systolic: 134.7±17.4 Diastolic: 75.0±10.6 Total Cholesterol (mg/dl): LDL: 100.7±32.1 HDL: 41.9±111.1 BMI: 32.5±5.4 Without diabetic retinopathy (%):50.6	RCT USA and Canada	**Glycemic-control intervention** Intensive glycemic control (targeting HbA1c level of 6.0%) vs. Standard control (target of 7.0–7.9%)
	Blood pressure study	Patients with type 2 diabetes Female (%): 47.9 Mean age: 61.3±6.1	Patients with type 2 diabetes Female (%): 45.3 Mean age: 61.5±6.6	RCT USA and Canada	**Blood-pressure-control intervention**

	Baseline and Follow-up (4 years)# IG: 647 CG: 616	Duration of diabetes (year): 10.1±7.0 HbA1c (%): 8.4±1.1 Blood pressure (mm Hg): Systolic: 138.0±16.7 Diastolic: 76.3±10.5 Total Cholesterol (mg/dl): LDL: 107.4±37.0 HDL: 46.3±12.8 BMI: 32.7±5.7 Without diabetic retinopathy (%): 50.9	Duration of diabetes (year): 10.3±7.5 HbA1c (%): 8.2±1.0 Blood pressure (mm Hg): Systolic: 139.0±14.7 Diastolic: 76.8±9.9 Total Cholesterol (mg/dl): LDL: 104.1±33.5 HDL: 46.1±13.8 BMI: 32.2±5.3 Without diabetic retinopathy (%): 47.9		Intensive systolic blood-pressure control (<120 mm Hg) vs. Standard systolic blood-pressure control (<140 mm Hg)
	Lipid study Baseline and Follow-up (4 years)# IG: 806 CG: 787	Patients with type 2 diabetes Female (%): 30.6 Mean age: 61.9±6.2 Duration of diabetes (year): 9.7±6.8 HbA1c (%): 8.2±1.0 Blood pressure (mm Hg): Systolic: 131.5±17.0 Diastolic: 73.7±10.5 Total Cholesterol (mg/dl): LDL: 96.5±29.7 HDL: 38.6±7.8 BMI: 32.3±5.5 Without diabetic retinopathy (%): 53.2	Patients with type 2 diabetes Female (%): 32.3 Mean age: 61.5±6.5 Duration of diabetes (year): 9.8±7.2 HbA1c (%): 8.2±1.0 Blood pressure (mm Hg): Systolic: 131.1±17.5 Diastolic: 73.6±10.5 Total Cholesterol (mg/dl): LDL: 97.0±30.1 HDL: 38.5±7.9 BMI: 32.6±5.4 Without diabetic retinopathy (%): 50.6	RCT USA and Canada	**Lipid-control intervention** Fenofibrate (160mg/day), to decrease triglyceride levels and to increase HDL cholesterol levels vs. Placebo
Kumamoto, 1995	**Primary-prevention cohort (no retinopathy)** Baseline and follow-up (6 years)+:IG:26 CG: 25	Patients with type 2 diabetes Female (%): 46.2 Mean age: 47±9 Duration of diabetes (year): 6.2±5.0 HbA1c (%): 9.2±1.8 Blood pressure (mm Hg): Systolic: 119±9 Diastolic: 69±6 Total Cholesterol (mg/dl): LDL: -	Patients with non-insulin-dependent diabetes Female (%): 52 Mean age: 49±14 Duration of diabetes (year): 6.7±5.3 HbA1c (%): 8.9±1.8 Blood pressure (mm Hg): Systolic: 121±14 Diastolic: 70±7 Total Cholesterol (mg/dl):	RCT Japan	**Glycemic-control intervention** Multiple insulin injection treatment vs. Conventional insulin injection treatment

		HDL: 50±14 BMI: 21.7±1.8 Without diabetic retinopathy (%): 100	LDL: - HDL: 53±14 BMI: 21.2±2.3 Without diabetic retinopathy (%): 100		
	Secondary-intervention cohort (patients with simple retinopathy) Baseline and follow-up (6 years)†:IG:26 CG: 25	Patients with type 2 diabetes Female (%): 53.9 Mean age: 49±13 Duration of diabetes (year): 10.2±4.2 HbA1c (%): 9.4±1.8 Blood pressure (mm Hg): Systolic: 121±11 Diastolic: 70±8 Total Cholesterol (mg/dl): LDL: - HDL: 52±19 BMI: 19.3±1.7 Without diabetic retinopathy (%): 0	Patients with non-insulin-dependent diabetes Female (%): 56 Mean age: 52±15 Duration of diabetes (year): 10.3±4.9 HbA1c (%): 9.0±1.9 Blood pressure (mm Hg): Systolic: 123±9 Diastolic: 70±7 Total Cholesterol (mg/dl): LDL: - HDL: 55±23 BMI: 19.2±2.8 Without diabetic retinopathy (%): 0	RCT Japan	**Glycemic-control intervention** Multiple insulin injection treatment vs. Conventional insulin injection treatment
Tovi, 1998	Baseline and Follow-up (1 year)‡ IG: 19 CG: 16	Patients with type 2 diabetes Female (%): 57.9 Mean age: 73±5 Duration of diabetes (year): 12±7 HbA1c (%): 9.3±1.4 Blood pressure (mm Hg): Systolic: 155±17 Diastolic: 78±10 Total Cholesterol (mg/dl): LDL: - HDL: - BMI: 26.3±4.6 Without diabetic retinopathy (%): 26.3	Patients with type 2 diabetes Female (%): 56.3 Mean age: 77±6 Duration of diabetes (year): 11±7 HbA1c (%): 9.1±1.1 Blood pressure (mm Hg): Systolic: 158±17 Diastolic: 80±9 Total Cholesterol (mg/dl): LDL: - HDL: - BMI: 28.3±4.3 Without diabetic retinopathy (%): 56.2	RCT Sweden	**Glycemic-control intervention** Insulin treatment vs. sulphonylurea treatment

Steno study, 1999	Baseline: IG: 80 CG: 80 Follow-up (3.8±0.3 years): IG: 73 CG: 76	Patients with type 2 diabetes Female (%): 21.3 Mean age: 54.9±7.2 Duration of diabetes (year): 5.5 (IQR 2.0-8.8) HbA1c (%): 8.4±1.6 Blood pressure (mm Hg): Systolic: 149±19 Diastolic: 86±11 Total Cholesterol (mg/dl): LDL: 133±36 HDL: 40±9 BMI: male 29.3±3.6, female 31.1±4.5 Without diabetic retinopathy (%): 72.5	Patients with type 2 diabetes Female (%): 30 Mean age: 55.2±7.2 Duration of diabetes (year): 6.0 (IQR 4.0-10.0) HbA1c (%): 8.8±1.7 Blood pressure (mm Hg): Systolic: 146±20 Diastolic: 85±10 Total Cholesterol (mg/dl): LDL: 137±37 HDL: 39±11 BMI: male 30.3±5.3, female 28.9±3.8 Without diabetic retinopathy (%): 73.8	Randomized open parallel trial Denmark	**Multifactorial intervention** Intensified multifactorial intervention (<140/85 mmHg, HbA1c<6.5%, diet, exercise, smoking intervention etc., if patients could not reach the targets of blood pressure and blood glucose after 3 months, stepwise approaches were adopted based on patients' situation.) vs. Standard intervention (<160/95 mmHg, HbA1c<7.5% etc.)
Steno 2 study, 2003	Baseline: IG: 80 CG: 80 Follow-up (7.8 years, range 6.9 to 8.8): IG: 67 CG: 63	Patients with type 2 diabetes Female (%): 21.3 Mean age: 54.9±7.2 Duration of diabetes (year): 5.5 (IQR 2.0-8.8) HbA1c (%): 8.4±1.6 Blood pressure (mm Hg): Systolic: 149±19 Diastolic: 86±11 Total Cholesterol (mg/dl): LDL: 133±36 HDL: 40±9 BMI: male 29.3±3.6, female 31.1±4.5 Without diabetic retinopathy (%): 72.5	Patients with type 2 diabetes Female (%): 30 Mean age: 55.2±7.2 Duration of diabetes (year): 6.0 (IQR 4.0-10.0) HbA1c (%): 8.8±1.7 Blood pressure (mm Hg): Systolic: 146±20 Diastolic: 85±10 Total Cholesterol (mg/dl): LDL: 133±36 HDL: 40±9 BMI: male 30.3±5.3, female 28.9±3.8 Without diabetic retinopathy (%): 73.8	Randomized open parallel trial Denmark	**Multifactorial intervention** Intensified multifactorial intervention (<140/85 mmHg, HbA1c<6.5%, diet, exercise, smoking intervention etc., if patients could not reach the targets of blood pressure and blood glucose after 3 months, stepwise approaches were adopted based on patients' situation.) vs. Standard intervention (<160/95 mmHg, HbA1c<7.5% etc.)
Rachmani, R., 2002	Baseline: IG:71 CG:70 Follow-up (4 years):	Patients with type 2 diabetes Female (%): 49.3 Mean age: 57.4±4.2 Duration of diabetes (year): 6.2±2.5	Patients with type 2 diabetes Female (%): 52.9 Mean age: 56.8±4.0 Duration of diabetes (year): 6.3±1.9	RCT Israel	**Multifactorial intervention** Intensive management of risk parameters in diabetic patients, Patient Participant

	IG:64 CG:65	HbA1c (%):9.5±1.6 Blood pressure (mm Hg): Systolic: 162±7.3 Diastolic: 96±2.4 Total Cholesterol (mg/dl): LDL: 146±10 HDL: 38±3 BMI: 28.4±2.4 Without diabetic retinopathy (%):84.5	HbA1c (%):9.6±1.9 Blood pressure (mm Hg): Systolic: 160±6.9 Diastolic: 95±2.0 Total Cholesterol (mg/dl): LDL: 148±9 HDL: 39±4 BMI: 28.7±2.3 Without diabetic retinopathy (%):85.7		Programme (PP group, sharing the therapeutic responsibility with patients) vs. Standard annual consultation In PP group, the patients were told that reaching and maintaining the desired levels of blood pressure, LDL-C and haemoglobin A1c (HbA1c) as well as compliance with medications were their responsibility. For most patients the target values were set at 130/85 mmHg, 100 mg/dl and 7%, respectively. The patients wrote down the individually recommended body weight they were encouraged to reach (based on a BMI < 25 for males and < 24 for females) through a core, age and gender-adjusted fitness programme based on walking four to five times a week. They were given the option to initiate a follow-up visit or a telephone conversation with the consultant when they needed advice.
PREDIMED study, 2015	Baseline and Follow-up (6 years), two intervention groups: IG(MedDiet+EVOO): 1282	Patients with type 2 diabetes MedDiet+EVOO/ MedDiet+Nuts Female (%): 55.2/48.1 Mean age: 67.5±6.2/67.1±6.1 Duration of diabetes (year): -	Patients with type 2 diabetes Female (%): 54.6 Mean age: 67.5±6.4 Duration of diabetes (year): - HbA1c (%):-	RCT Spain	**Dietary-control intervention** Mediterranean diet (MedDiet) supplemented with extra virgin olive oil (MedDiet+EVOO) vs. MedDiet

	IG(MedDiet+Nuts): 1142 CG:1190	HbA1c (%):- Blood pressure (mm Hg): Systolic: - Diastolic: - Total Cholesterol (mg/dl): LDL: - HDL: 50.0(43.0, 59.0)/49.6(42.2,58.2) BMI: 29.8±3.8/29.5±3.9 Without diabetic retinopathy (%):100	Blood pressure (mm Hg): Systolic: - Diastolic: - Total Cholesterol (mg/dl): LDL: - HDL: 50.0(40.0, 59.1) BMI: 30.2±4.3 Without diabetic retinopathy (%):100		supplemented with mixed nuts (MedDiet+Nuts) vs. Low-fact control diet
UKPDS 69, 2004	Baseline IG: 758 CG: 390 Follow-up (7.5 years) IG: 300 CG: 152	Patients with type 2 diabetes Female (%): 46 Mean age: 56.4±8.1 Duration of diabetes (interquartile range, year): 2.7(1.0-4.2) HbA1c (%):6.9±1.7 Blood pressure (mm Hg): Systolic: 159±20 Diastolic: 94±10 Total Cholesterol (mmol/l): LDL: 3.6±1.1 HDL: 1.10±0.27 BMI: 29.8±5.5 Without diabetic retinopathy (%): 81.4	Patients with type 2 diabetes Female (%): 42 Mean age: 56.5±8.1 Duration of diabetes (interquartile range, year): 2.5(1.0-4.4) HbA1c (%): 6.8±1.5 Blood pressure (mm Hg): Systolic: 160±18 Diastolic: 94±9 Total Cholesterol (mmol/l): LDL: 3.6±1.1 HDL: 1.10±0.28 BMI: 29.3±5.5 Without diabetic retinopathy (%): 80	RCT England	**Blood-pressure-control intervention** Tight control of blood pressure (aim<150/85mm Hg) vs. Less tight control of blood pressure (aim< 180/105 mmHg)
VADT, 2016	Baseline and follow-up (5 years) [&]: IG: 433 CG: 425	Veterans with Type 2 Diabetes Female (%): 3.7 Mean age: 60±8 Duration of diabetes (year): 11.5±7.8 HbA1c (%):9.3±1.4 Blood pressure (mm Hg): Systolic: 132±17 Diastolic: 76±10 Total Cholesterol (mmol/l): LDL: 2.8±0.83 HDL: 0.93±0.23 BMI: 32±4 Without diabetic retinopathy (%):-	Veterans with Type 2 Diabetes Female (%): 3.1 Mean age: 60±8 Duration of diabetes (year): 11.5±6.6 HbA1c (%):9.4±1.5 Blood pressure (mm Hg): Systolic: 131±17 Diastolic: 76±10 Total Cholesterol (mmol/l): LDL: 2.8±0.86 HDL: 0.93±0.28BMI: 31±4 Without diabetic retinopathy (%):-	RCT USA	**Glycemic-control intervention** Intensive glucose control (started on maximal dose) vs. Standard control (started on half the maximal dose)

ACCORDION Eye Study [$], 2016	**Glycemic control study** Baseline and follow-up (8 years): IG:658 CG:652	Patients with type 2 diabetes Female (%):36.5 Mean age: 61.4±5.9 Duration of diabetes (year): 9.6±6.7 HbA1c (%): 8.1±0.9 Blood pressure (mm Hg): Systolic: 132.7±16.1 Diastolic: 74.7±10.1 Total Cholesterol (mg/dl): LDL: 97.7±32.7 HDL: 41.9±11.0 BMI: 32.4±5.2 Without diabetic retinopathy (%): 53.2	Patients with type 2 diabetes Female (%):38.8 Mean age: 61.2±5.7 Duration of diabetes (year): 10.1±6.9 HbA1c (%): 8.2±1.0 Blood pressure (mm Hg): Systolic: 133.4±16.7 Diastolic: 74.7±10.6 Total Cholesterol (mg/dl): LDL: 100.7±32.6 HDL: 41.4±10.3 BMI: 32.3±5.6 Without diabetic retinopathy (%): 51.7	RCT USA Canada	**Glycemic-control intervention** Intensive glycemic control (targeting HbA1c level of 6.0%) vs. Standard control (target of 7.0–7.9%)
	Blood pressure study Baseline and follow-up (8 years): IG:280 CG:268	Patients with type 2 diabetes Female (%):45.4 Mean age: 61.3±5.8 Duration of diabetes (year): 10.5±6.8 HbA1c (%): 8.3±1.0 Blood pressure (mm Hg): Systolic: 136.8±15.9 Diastolic: 74.7±10.1 Total Cholesterol (mg/dl): LDL: 106.1±36.4 HDL: 46.2±12.5 BMI: 32.3±5.6 Without diabetic retinopathy (%): 51.1	Patients with type 2 diabetes Female (%):45.5 Mean age: 61.1±6.1 Duration of diabetes (year): 10.1±7.3 HbA1c (%): 8.2±1.0 Blood pressure (mm Hg): Systolic: 138.6±15.9 Diastolic: 74.7±10.6 Total Cholesterol (mg/dl): LDL: 102.1±34.4 HDL: 45.9±12.8 BMI: 32.4±5.3 Without diabetic retinopathy (%): 50.0	RCT USA Canada	**Blood-pressure-control intervention** Intensive blood pressure control (targeting systolic BP of 120mmHg) or standard treatment (140 mmHg)
	Lipid study Baseline and follow-up (8 years): IG:399 CG:363	Patients with type 2 diabetes Female (%):27.6 Mean age: 61.8±5.8 Duration of diabetes (year): 9.8±6.5 HbA1c (%): 8.2±1.0 Blood pressure (mm Hg):	Patients with type 2 diabetes Female (%):36.9 Mean age: 61.1±5.6 Duration of diabetes (year): 9.4±6.6 HbA1c (%): 8.1±0.9 Blood pressure (mm Hg):	RCT USA Canada	**Lipid-control intervention** Fenofibrate (160mg/day), to decrease triglyceride levels and to increase HDL cholesterol levels vs. Placebo

		Systolic: 129.9±15.6 Diastolic: 73.6±10.0 Total Cholesterol (mg/dl): LDL: 94.9±30.4 HDL: 38.2±7.4 BMI: 32.0±5.4 Without diabetic retinopathy (%): 54.9	Systolic: 129.4±16.8 Diastolic: 73.2±10.5 Total Cholesterol (mg/dl): LDL: 96.4±29.8 HDL: 38.9±7.6 BMI: 32.6±5.3 Without diabetic retinopathy (%): 52.6		
ADVANCE, 2008	Baseline: IG: 5571 CG: 5569 Follow-up (median: 5 years): IG: 4828 CG: 4741	Patients with type 2 diabetes Female (%):42.6 Mean age: 66±6 Duration of diabetes (year): 7.9±6.3 HbA1c (%): 7.51±1.57 Blood pressure (mm Hg): Systolic: 145.0±21.7 Diastolic: 80.8±11.0 Total Cholesterol (mmol/l): LDL: 3.12±1.04 HDL: 1.26±0.35 BMI: 28±5 Without diabetic retinopathy (%): -	Patients with type 2 diabetes Female (%):42.3 Mean age: 66±6 Duration of diabetes (year): 8.0±6.4 HbA1c (%): 7.52±1.54 Blood pressure (mm Hg): Systolic: 145.0±21.4 Diastolic: 80.5±10.8 Total Cholesterol (mg/dl): LDL: 3.11±1.02 HDL: 1.25±0.35 BMI: 28±5 Without diabetic retinopathy (%):-	RCT Asia, Australasia, Europe, and North America	**Glycemic-control intervention** Intensive blood glucose control (target HbA1c value, ≤6.5%) vs. Standard glucose control
AdRem Study @, 2009	Baseline: IG: 791 CG: 811 Follow-up (4.1 years): IG: 630 CG: 611	Patients with type 2 diabetes Female (%): 38.1 Mean age: 65.6±6.0 Duration of diabetes: 6 (IQR 2-11) HbA1c (%):7.4±1.5 Blood pressure (mm Hg): Systolic: 142.7±22.2 Diastolic: 79.6±10.9 Total Cholesterol (mmol/l): LDL: - HDL: - BMI: - Without diabetic retinopathy (%): 49.7	Patients with type 2 diabetes Female (%): 39.3 Mean age: 65.6±5.7 Duration of diabetes: 6 (IQR 2-11) HbA1c (%): 7.4±1.5 Blood pressure (mm Hg): Systolic: 142.7±21.2 Diastolic: 79.0±10.8 Total Cholesterol (mmol/l): LDL: - HDL: - BMI: - Without diabetic retinopathy (%): 51.3	RCT Asia, Australasia, Europe, and North America	**Glycemic-control intervention** Intensive blood glucose control (target HbA1c value, ≤6.5%) vs. Standard glucose control

California Medi-Cal Study, 2005	Baseline IG: 61 CG: 49 Follow-up (mean: 1.9 years) IG: 48 CG: 34	Patients with type 2 diabetes but with no retinopathy Female (%): 75.4 Mean age: 53.5±12.4 Duration of diabetes (year): 7.3±5.4 HbA1c (%): 9.6±1.6 Blood pressure (mm Hg): Systolic: - Diastolic: - Total Cholesterol (mmol/l): LDL: - HDL: - BMI: - Without diabetic retinopathy (%): 100	Patients with type 2 diabetes but with no retinopathy Female (%): 69.4 Mean age: 53.5±13.9 Duration of diabetes (year): 7.5±8.3 HbA1c (%): 9.7±1.8 Blood pressure (mm Hg): Systolic: - Diastolic: - Total Cholesterol (mmol/l): LDL: - HDL: - BMI: - Without diabetic retinopathy (%): 100	RCT USA	**Multifactorial intervention** Intensive diabetes case management (subjects were seen or contacted by the case management staff at varying intervals according to the need at least monthly to lower blood glucose) in addition to standard care vs. Control group (standard care, blood glucose determination was collected at 6-month intervals, and contact between study staff and participants was generally limited to that needed to assure collection)
Lifestyle intervention study, 2002	Baseline IG: 56 CG: 56 Follow-up (mean:4.3 years) IG: 45 CG: 42	Patients with type 2 diabetes Female (%): 51.8 Mean age (year, range): 62.0, 35-80 Duration of diabetes (year, range): 9.4, 1-23 HbA1c (%): 7.4±1.4 Blood pressure (mm Hg): Systolic: 160±26 Diastolic: 95±11 Total Cholesterol (mmol/l): LDL: 5.84±1.11 HDL: 1.27±0.31 BMI: 29.8±4.5 Without diabetic retinopathy (%): -	Patients with type 2 diabetes Female (%): 39.3 Mean age (year, range): 61.0, 43-78 Duration of diabetes (year, range): 9.8, 1-39 HbA1c (%): 7.4±1.4 Blood pressure (mm Hg): Systolic: 151±19 Diastolic: 92±10 Total Cholesterol (mmol/l): LDL: 5.46±0.93 HDL: 1.32±0.31 BMI: 27.9±4.5 Without diabetic retinopathy (%): -	RCT Italy	**Multifactorial intervention** Systemic group education (Educational sessions were held every 3 months, with one to two physicians and an educationist acting as facilitators. The programme included: the burden of overweight, choosing food, meal planning, physical exercise, checking and improving metabolic control, smoke cessation, assuming medication and preventing complications) vs. Control group (individual consultations and education scheduled for 3-monthly visits, or as frequently as

					necessary, in the general diabetes clinic by the same physicians in charge of the group sessions)
VA CSDM, 1996	Baseline: IG: 75 CG: 78 Follow-up (2 years): IG: 63 CG: 67	Male patients with type 2 diabetes Female (%): 0 Mean age: 60.4±0.7 Duration of diabetes: 8.0±0.4 HbA1c (%):9.3±0.2 Blood pressure (mm Hg): Systolic: 136.1±1.8 Diastolic: 80.8±1.0 Total Cholesterol (mmol/l): LDL: - HDL: - BMI: - Without diabetic retinopathy (%): 38.7	Male patients with type 2 diabetes Female (%): 0 Mean age: 59.9±0.8 Duration of diabetes: 7.7±0.5 HbA1c (%): 9.5±0.2 Blood pressure (mm Hg): Systolic: 134.5±1.7 Diastolic: 80.9±0.9 Total Cholesterol (mmol/l): LDL: - HDL: - BMI: - Without diabetic retinopathy (%): 37.2	Randomized prospective trial USA	**Glycemic-control intervention** Intensive control group (the goal of intensive therapy was to obtain an HbAlc within two standard deviations of the mean of nondiabetic subjects (4.0-6.1%).) vs. Standard control group (The goal of standard therapy was good general medical care and well-being and avoiding excessive hyperglycemia, glycosuria, ketonuria, or hypoglycemia.)

* In ACCORD Eye Study, 3472 participants were eligible for follow-up at baseline and 2856 (82.5%) had both baseline and follow-up data. Baseline data of 2856 patients were provided.

A total of 1263 ACCORD Eye study participants were also enrolled in the ACCORD Blood Pressure Study.

† In this study, there were 55 participants in each cohort respectively and 102 remained in the study after six years with 51 in each cohort. Baseline data of 102 patients were provided.

‡ There were 40 patients enrolled in this study, 22 in intervention group and 18 in control group. Only 35 patients continued the one year follow-up. Baseline data of 35 patients were provided.

$ After the ACCORD trial was completed, surviving participants who were invited for follow-up in the main study and who had fundus photographs at baseline were invited to have additional photographs 8 years after randomization. The effects of a mean of 3.7 years of intensive glycemic control and 5 years of intensive blood pressure control and/or fenofibrate on the progression of diabetic retinopathy during 8 years of follow-up in the ACCORD Follow-On (ACCORDION) Eye Study are reported here.

& Reported here are the data from 858 of 1,791 subjects in the VADT who completed 7-fielstereo fundus photographs at baseline and 5 years later. The individuals included in this study were largely representative of the VADT cohort as a whole

@ The results of the ADVANCE Retinal Measurements (AdRem) study, a substudy of ADVANCE. In addition to the inclusion and exclusion criteria of ADVANCE, patients were excluded from AdRem if they had had a previous ophthalmological intervention procedure (such as laser coagulation treatment or vitrectomy) or if it was unlikely that good quality stereo photographs could be taken, because of severe cataract or pupils that did not dilate to at least 4 mm.

Supplementary Table S2 Key Data in Studies

DR Condition	Study	Intervention Group		Control Group	
		Event	No event	Event	No event
New onset DR among patients with type 2 diabetes	ABCD trail, 2002	38	60	42	59
	Kumamoto, 1995	2	24	8	17
	Tovi, 1998	0	5	2	7
	Rachmani, R., 2002	6	47	17	38
	PREDIMED study, MedDiet+EVOO, 2015	22	1260	32	1158
	PREDIMED study, MedDiet+Nuts, 2015	20	1122	32	1158
	VADT, 2016	52	76	62	73
	California Medi-Cal Study, 2005	5	43	10	24
	UKPDS 69, 2004	63	108	40	36
	Lifestyle intervention study, 2002	4	29	10	18
	VA CSDM, 1996	8	19	5	20
Worsening DR among patients with type 2 diabetes	ABCD trail, 2002	33	64	46	55
	Kumamoto, 1995	5	21	11	14
	Tovi, 1998	5	9	2	5
	UKPDS 69, 2004	39	90	38	38
	VADT, 2016	54	251	66	224
	Lifestyle intervention study, 2002	0	12	3	11
	VA CSDM, 1996	13	23	17	25
DR Progression among patients with type 2 diabetes*	Steno study, 1999	19	54	33	43
	Steno study 2, 2003	38	29	51	12
	ACCORDION Eye Study, 2016-Glycemic control study	38	620	83	569
	ACCORDION Eye Study, 2016-Blood pressure study	21	259	16	252
	ACCORDION Eye Study, 2016-Lipid study	47	352	37	326
	ACCORD Eye Study, 2010-Glycemic control study	104	1325	149	1278
	ACCORD Eye Study, 2010-Blood pressure study	67	580	64	552
	ACCORD Eye Study, 2010-Lipid study	52	754	80	707
	ADVANCE, 2008	332	5201	349	5191
	AdRem Study, 2009	88	542	99	512

* For studies failing to provide distinctive data for new onset and worsening DR, the term "DR Progression" was adopted to cover both new onset and worsening DR

DR, diabetic retinopathy

Supplementary Table S3 Diagnosis method and progression definition of DR

Study	Diagnosis method of DR	Worsening or progression of DR
ABCD trail, 2002	Retinopathy was staged using the Modified Airlie House Classification of Diabetic Retinopathy. Seven-field stereoscopic fundus photographs were taken on-site at baseline then at year 2 and 5 by a technician trained by the Reading Center. The graders used the protocol of the Early Treatment Diabetic Retinopathy Study (ETDRS).	The worsening of clinically important retinopathy is defined as a change of at least two steps from baseline measurements.
ACCORD Eye Study, 2010	The study consisted of two comprehensive, standardized eye examinations conducted by a study ophthalmologist or optometrist, along with fundus photography of seven standard stereoscopic fields, at baseline and 4 years of follow-up. The fundus photographs were evaluated on the basis of the photographic standards defined for the Early Treatment Diabetic Retinopathy Study (ETDRS) and graded according to an abbreviated and modified version of the ETDRS.	The progression of diabetic retinopathy is defined as a change of at least three steps on the ETDRS Severity Scale.
ACCORDION Eye Study, 2016	Same as above	Same as above
Kumamoto, 1995	All of the patients had direct ophthalmoscopy, with pupils dilated. Fundoscopic findings were evaluated by at least 2 examiners (an ophthalmologist and an internist) followed by color fundus photography and fluorescein angiography. The degrees of retinopathy were determined by the 2 eye examiners for each patient in accordance with the ETDRS interim scale.	The worsening of retinopathy were defined as the change of at least 2 steps.
Tovi, 1998	Eye-ground changes were documented by initial ophthalmological examinations. The examinations included measurements of visual acuity and intraocular pressure. Stereofundic photographs of the optic disc, the macular area, the area temporal to the macula and nasal to the optic disc, and other areas of interest were taken for all patients. Evaluations of fundic photographs were performed blind by the ophthalmologist (S.O.I.). Grading of the patients' retinopathy was based on the alternative classification of the Wisconsin Epidemiologic Study of Diabetic Retinopathy.	The progression of retinopathy was defined as a two-step increase in severity.
Steno study, 1999	Retinal photographs of two 45–50°C fields (maculatemporal and disc-nasal) were taken in both eyes through dilated pupils. The photographs were graded by two independent, ophthalmologists, masked to treatment allocation, according to the EURODIAB six-level grading scale.	Progression of retinopathy was an increase of at least one level in any eye.
Steno 2 study, 2003	Same as above	Same as above
Rachmani, R., 2002	Patients of both groups were seen by one of the authors on four annual follow-up visits during which relevant data were reviewed and letters were written to the primary care physicians. The data available at each visit included clinic and home blood pressure values, BMI, blood levels of HbA1c, total cholesterol, LDL, HDL triglycerides, serum creatinine, serum	N/A

	albumin, uric acid, urinary albumin/creatinine ratio and a written report of fundoscopy by an ophthalmologist.	
PREDIMED study, 2015	New onset diabetic retinopathy was defined by the medical diagnosis made by an ophthalmologist of any nonproliferative or proliferative diabetic retinopathy, or laser photocoagulation treatment for diabetic retinopathy, as reported in the medical charts. These reports and all relevant documentation, including medical records made by ophthalmologists, were sent to the PREDIMED members of the Clinical Adjudication Events Committee.	N/A
UKPDS 69, 2004	Retinal colour photographs of four standard 30° fields per eye (nasal, disc, macula, and temporal to macular fields) were taken plus stereophotographs of the macula. Repeat photography was arranged if the quality of the photograph was unsatisfactory. Retinal photographs were assessed at a central grading centre for the presence or absence of diabetic retinopathy. Any fields with retinopathy were graded by two further senior independent assessors using a modified ETDRS final scale.	The worsening of retinopathy is defined as a change of at least two steps.
VADT, 2016	Patients underwent a standard annual ophthalmologic examination. Stereo seven-field fundus photographs were obtained at baseline and at 5 years by certified photographers. The 23-step Early Treatment Diabetic Retinopathy Study (ETDRS) grading scale was used to define progression to new proliferative diabetic retinopathy.	The worsening of retinopathy was defined as a 2-step increase on the scale.
ADVANCE, 2008	Seven standard field stereoscopic photographs of the left and right eyes were taken with 35 mm high-quality colour films (Kodak EPR64 135-36), according to the Early Treatment of Diabetic Retinopathy Study (ETDRS) protocol.	The progression of retinopathy was defined as progression of ≥2 steps in ETDRS classification with laser coagulation therapy during follow-up as the final step in ETDRS classification.
AdRem Study, 2009	Seven standard field stereoscopic photographs of the left and right eyes were taken with 35 mm high-quality colour films (Kodak EPR64 135-36), according to the Early Treatment of Diabetic Retinopathy Study (ETDRS) protocol. The seven fields included one centred on the optic disc, one centred on the macula, one temporal to the macula, and two superior and two inferior fields. In patients with non-gradeable images according to strict criteria, repeat photographs were sought. The ETDRS classification was slightly modified in the UKPDS, and this modified classification was used in the AdRem study. Detected lesions were graded in comparison with the ETDRS final scale standard photographs.	The progression of retinopathy was defined as progression of ≥2 steps in ETDRS classification with laser coagulation therapy during follow-up as the final step in ETDRS classification.
California Medi-Cal Study, 2005	One photograph was taken of each eye with a Canon CR4-45° nonmydriatic camera. Photographs were taken in a dark room to facilitate dilatation of the pupils and improve the quality of the photographs. Additionally, at the Los Angeles site, pupils were dilated before taking the photos. The retinal field	N/A

	photographed was identical at both sites and consisted of the area nasal to the disc and temporal to the macula and the superior and inferior arcades. All photographs were labeled with only the patient's identification number and were sent for reading in Santa Barbara. Polaroid prints from the Canon camera were examined and graded by an experienced endocrinologist (L.J.) who, before this study, had readings verified by an ophthalmologist until agreement was virtually 100%. An overview grading was assigned for each eye at each examination using the Wisconsin Epidemiologic Study of Diabetic Retinopathy II/III–modified diabetic retinopathy levels, which used a modification of the Airlie House Criteria.	
Lifestyle intervention study, 2002	Diabetic retinopathy was assessed by indirect and direct ophthalmoscopy by a trained physician (MP) and color fundus photography of two 45° fields on 35 mm film (Elite Chrome 100 ASA, Eastman Kodak, Rochester, N.Y., USA), according to EURODIAB and European Screening Guidelines procedures. Rare microaneurysms and/or microhaemorrhages and/or isolated cotton wool spots at least one disc in diameter away from the fovea defined mild retinopathy. Lesions closer to the macula, and/or more advanced presentations defined more severe retinopathy.	Worsening of retinopathy was an increase of at least one level in any eye.
VA CSDM, 1996	To determine the incidence and progression of retinopathy in each eye, all of the fundus photographs were graded in a masked fashion using the Early Treatment Diabetic Retinopathy Study (ETDRS) adaptation of the modified Airlie House classification scheme that specifies 13 levels. Meanings of each level are shown in Table 2. Eyes that could not be graded for retinopathy levels because of opacities in the media or enucleation not related to diabetic retinopathy were classified as "cannot grade." In determining retinopathy levels for a participant, the eye with the higher level was given greater weight. For purposes of classification, if retinopathy severity could not be graded in an eye, this eye was considered to have the same score as the participants other eye.	Worsening was defined as an increase in the retinopathy severity level of two or more steps.

DR, diabetic retinopathy

Supplementary Table S4 Risk of Bias

Study	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias
ABCD trail, 2002	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk
ACCORD Eye Study, 2010	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk
ACCORDION Eye Study, 2016	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk
Kumamoto, 1995	Unclear risk	High risk	Unclear risk	Low risk	Low risk	Low risk
Tovi, 1998	Unclear risk	High risk	Unclear risk	Low risk	Unclear risk	Low risk
Steno study, 1999	Unclear risk	High risk	Unclear risk	Low risk	Unclear risk	Low risk
Steno 2 study, 2003	Unclear risk	High risk	Unclear risk	Low risk	Unclear risk	Low risk
Rachmani, R., 2002	Low risk	High risk	Unclear risk	Low risk	Unclear risk	Low risk
PREDIMED study, 2015	Low risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk
UKPDS 69, 2004	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk
VADT, 2016	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk
ADVANCE, 2008	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk
AdRem Study, 2009	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk
California Medi-Cal Study, 2005	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk
Lifestyle intervention, 2002	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk	Low risk
VA CSDM, 1996	Unclear risk	High risk	Unclear risk	Low risk	Low risk	Low risk

Supplementary Table S5 GRADE Evidence Profile: New onset DR

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Interventions targeting modifiable risk factors of DR	Control	Relative (95% CI)	Absolute		
New Onset DR (follow-up 1 to 7.5 years)												
11	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[2]	220/3013 (7.3%)	260/2868 (9.1%)	OR 0.60 (0.45 to 0.79)	34 fewer per 1000 (from 18 fewer to 48 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
New Onset DR: Blood-pressure-control intervention (follow-up 5 to 7.5 years)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	101/269 (37.5%)	82/177 (46.3%)	OR 0.68 (0.41 to 1.14)	93 fewer per 1000 (from 202 fewer to 33 more)	⊕⊕⊕O MODERATE	IMPORTANT
New Onset DR: Glycemic-control intervention (follow-up 1-6 years)												
4	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	62/186 (33.3%)	77/194 (39.7%)	OR 0.70 (0.31 to 1.57)	82 fewer per 1000 (from 227 fewer to 111 more)	⊕⊕OO LOW	IMPORTANT
New Onset DR: Dietry-control intervention (follow-up 6 years)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	42/2424 (1.7%)	64/2380 (2.7%)	OR 0.64 (0.43 to 0.95)	10 fewer per 1000 (from 1 fewer to 15 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
New Onset DR: Multifactorial intervention (follow-up 1.9 to 4.3 years)												
3	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	15/134 (11.2%)	37/117 (31.6%)	OR 0.27 (0.14 to 0.53)	205 fewer per 1000 (from 119	⊕⊕⊕O MODERATE	IMPORTANT

										fewer to 255 fewer)		
New Onset DR: Follow-up<2 years (follow-up 1 to 2 years)												
3	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	13/80 (16.3%)	17/68 (25%)	OR 0.59 (0.15 to 2.34)	86 fewer per 1000 (from 202 fewer to 188 more)	⊕⊕⊕O MODERATE	IMPORTANT
New Onset DR: Follow-up 2-5 years (follow-up 4 to 5 years)												
4	randomised trials	no serious risk of bias[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	100/312 (32.1%)	131/319 (41.1%)	OR 0.59 (0.34 to 1.02)	119 fewer per 1000 (from 219 fewer to 5 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
New Onset DR: Follow-up >5 years (follow-up 6 to 7.5 years)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	105/2595 (4%)	104/2456 (4.2%)	OR 0.57 (0.42 to 0.78)	18 fewer per 1000 (from 9 fewer to 24 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT

[1] Four studies had high risk of performance bias [Kumamoto, 1995; Tovi, 1998; Rachmani, R., 2002; VA CSDM, 1996]
[2] 11 RCTs
[3] Only two studies
[4] Three studies had high risk of performance bias [Kumamoto, 1995; Tovi, 1998; VA CSDM, 1996]
[5] One study had high risk of performance bias [Rachmani, R., 2002]
[6] Two studies had high risk of performance bias [Tovi, 1998; VA CSDM, 1996]
VA CSDM, 1996
DR, diabetic retinopathy

Supplementary Table S6 GRADE Evidence Profile: DR Worsening

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Interventions targeting modifiable risk factors of DR	Control	Relative (95% CI)	Absolute		
DR Worsening (follow-up 1 to 7.5 years)												
7	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[2]	149/619 (24.1%)	183/555 (33%)	OR 0.62 (0.47 to 0.80)	96 fewer per 1000 (from 47 fewer to 142 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
DR Worsening: Blood-pressure-control intervention (follow-up 5-7.5 years)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	72/226 (31.9%)	84/177 (47.5%)	OR 0.52 (0.34 to 0.78)	155 fewer per 1000 (from 61 fewer to 240 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
DR Worsening: Glycemic-control intervention (follow-up 1 to 6 years)												
4	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	77/381 (20.2%)	96/364 (26.4%)	OR 0.71 (0.50 to 1.00)	61 fewer per 1000 (from 112 fewer to 0 more)	⊕⊕OO LOW	IMPORTANT
DR Worsening: Multifactorial intervention (follow-up 4.3 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	0/12 (0%)	3/14 (21.4%)	not pooled	not pooled		not applicable
DR Worsening: Follow-up<2 years (follow-up 1 to 2 years)												
2	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	18/50 (36%)	19/49 (38.8%)	OR 0.91 (0.40 to	22 fewer per 1000 (from	⊕⊕OO LOW	IMPORTANT

									2.09)	186 fewer to 182 more)		
DR Worsening: Follow-up 2-5 years (follow-up 4.3 to 5 years)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	87/414 (21%)	115/407 (28.3%)	OR 0.68 (0.49 to 0.94)	71 fewer per 1000 (from 12 fewer to 121 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT
DR Worsening: Follow-up>5 years (follow-up 6 to 7.5 years)												
2	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[3]	none	44/155 (28.4%)	49/101 (48.5%)	OR 0.41 (0.24 to 0.69)	206 fewer per 1000 (from 91 fewer to 301 fewer)	⊕⊕OO LOW	IMPORTANT

[1] Three studies had high risk of performance bias [Kumamoto, 1995; Tovi, 1998; VA CSDM, 1996]

[2] 7 RCTs

[3] Only two studies

[4] Only one study

[5] Two studies had high risk of performance bias [Tovi, 1998; VA CSDM, 1996]

6 One study had high risk of performance bias [Kumamoto, 1995]

DR, diabetic retinopathy

Supplementary Table S7 GRADE Evidence Profile: DR Progression

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Interventions targeting modifiable risk factors of DR	Control	Relative (95% CI)	Absolute		
DR Progression (follow-up 3.8 to 8 years)												
10	randomised trials	no serious risk of bias	very serious[1]	no serious indirectness	no serious imprecision	none	747/9584 (7.8%)	862/9483 (9.1%)	OR 0.74 (0.59 to 0.92)	22 fewer per 1000 (from 7 fewer to 35 fewer)	⊕⊕OO LOW	CRITICAL
DR Progression: Blood-pressure-control intervention (follow-up 4 to 8 years)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	67/645 (10.4%)	64/616 (10.4%)	OR 1.05 (0.77 to 1.45)	5 more per 1000 (from 22 fewer to 40 more)	⊕⊕⊕O MODERATE	IMPORTANT
DR Progression: Glycemic-control intervention (follow-up 4 to 8 years)												
4	randomised trials	no serious risk of bias	very serious[1]	no serious indirectness	no serious imprecision	none	524/7592 (6.9%)	597/7578 (7.9%)	OR 0.71 (0.52 to 0.97)	22 fewer per 1000 (from 2 fewer to 36 fewer)	⊕⊕OO LOW	IMPORTANT
DR Progression: Lipid-control intervention (follow-up 4 to 8 years)												
2	randomised trials	no serious risk of bias	very serious[1]	no serious indirectness	serious[2]	none	99/1205 (8.2%)	117/1150 (10.2%)	OR 0.83 (0.44 to 1.59)	16 fewer per 1000 (from 54 fewer to 51 more)	⊕OOO VERY LOW	IMPORTANT
DR Progression: Multifactorial intervention (follow-up 3.8 years)												
2	randomised trials	no serious risk of	no serious inconsistency	no serious indirectness	serious[2]	none	57/140 (40.7%)	84/139 (60.4%)	OR 0.39 (0.23 to 0.65)	231 fewer per 1000 (from 106	⊕⊕⊕O MODERATE	IMPORTANT

		bias								fewer to 344 fewer)		
DR Progression: Follow-up 2-5 years (follow-up 3.8 to 5 years)												
7	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	no serious imprecision	none	700/9185 (7.6%)	825/9120 (9%)	OR 0.73 (0.59 to 0.91)	23 fewer per 1000 (from 7 fewer to 35 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
DR Progression: Follow-up >5 years (follow-up 8 years)												
3	randomised trials	no serious risk of bias	very serious[1]	no serious indirectness	no serious imprecision	none	47/399 (11.8%)	37/363 (10.2%)	OR 0.84 (0.39 to 1.80)	15 fewer per 1000 (from 60 fewer to 68 more)	⊕⊕OO LOW	IMPORTANT

[1] Substantial heterogeneity

[2] Only two studies

DR, diabetic retinopathy

Sensitivity Analysis (New onset diabetic retinopathy)

According to the results in Supplementary Figure S1, the sensitivity of the 11 studies was low.

Study	OR	[95% Conf. Interval]	% Weight
ABCD trail, 2002	0.890	0.505 1.569	14.66
Kumamoto, 1995	0.177	0.033 0.940	2.60
Tovi, 1998	0.273	0.011 6.892	0.73
Rachmani, R., 2002	0.285	0.102 0.795	6.19
PREDIMED study, MedD	0.632	0.365 1.094	15.26
PREDIMED study, MedD	0.645	0.367 1.135	14.74
VADT, 2016	0.806	0.494 1.314	17.37
California Medi-Cal	0.279	0.085 0.912	4.83
UKPDS 69, 2004	0.525	0.304 0.907	15.31
Lifestyle interventi	0.248	0.068 0.911	4.10
VA CSDM, 1996	1.684	0.467 6.068	4.21
D+L pooled OR	0.596	0.451 0.788	100.00

Supplementary Figure S1 Sensitivity Analysis Results (New onset diabetic retinopathy)

Publication Bias (New onset diabetic retinopathy)

According to Supplementary Figure S2, no publication bias was found.

Tests for Publication Bias

Begg's Test

adj. Kendall's Score (P-Q) = -11
Std. Dev. of Score = 12.85
Number of Studies = 11
z = -0.86
Pr > |z| = 0.392
z = 0.78 (continuity corrected)
Pr > |z| = 0.436 (continuity corrected)

Egger's test

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf. Interval]	
slope	-.0115156	.2718915	-0.04	0.967	-.6265769	.6035457
bias	-1.370224	.7259532	-1.89	0.092	-3.012444	.2719963

Supplementary Figure S2 Egger's and Begg's Test (New onset diabetic retinopathy)

Sensitivity Analysis (Diabetic retinopathy worsening)

According to the results in Supplementary Figure S3, the sensitivity of the 7 studies was low.

Study ommited	e^coef.	[95% Conf.	Interval]
ABCD trail, 2002	.60658848	.43794408	.84017473
Kumamoto, 1995	.63568246	.48507017	.83305925
Tovi, 1998	.60601652	.46412706	.79128337
UKPDS 69, 2004	.6727218	.5002678	.90462482
VADT, 2016	.53996104	.38023749	.76677847
Lifestyle intervention study, 2002	.62226039	.47724709	.81133658
VA CSDM, 1996	.59859693	.45420566	.78889
Combined	.615126	.47224055	.80124419

Supplementary Figure S3 Sensitivity Analysis Results (Diabetic retinopathy worsening)

Publication Bias (Diabetic retinopathy worsening)

According to Supplementary Figure S4, no publication bias was found.

Tests for Publication Bias

Begg's Test

adj. Kendall's Score (P-Q) = -3
Std. Dev. of Score = 6.66
Number of Studies = 7
z = -0.45
Pr > |z| = 0.652
z = 0.30 (continuity corrected)
Pr > |z| = 0.764 (continuity corrected)

Egger's test

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	-.317115	.2631359	-1.21	0.282	-.9935273	.3592973
bias	-.5471787	.7374261	-0.74	0.491	-2.442793	1.348435

Supplementary Figure S4 Egger's and Begg's Test (Diabetic retinopathy worsening)

Sensitivity Analysis ((Diabetic retinopathy progression)

According to the results in Supplementary Figure 5, the sensitivity of the 10 studies was low.

Study ommited	e^coef.	[95% Conf.	Interval]
Steno study, 1999	.76070899	.60672265	.95377713
Steno study 2, 2003	.77389759	.62554616	.95743132
ACCORDION Eye Study, 2016-Glycemic control study	.79420441	.64846182	.97270286
ACCORDION Eye Study, 2016-Blood pressure study	.70927691	.56384391	.89222175
ACCORDION Eye Study, 2016-Lipid study	.70137227	.55538791	.88572884
ACCORD Eye Study, 2010-Glycemic control study	.74302423	.57669914	.9573189
ACCORD Eye Study, 2010-Blood pressure study	.70751256	.55413181	.90334821
ACCORD Eye Study, 2010-Lipid study	.75331682	.59248894	.95780051
ADVANCE, 2008	.70374453	.54682726	.90569073
AdRem Study, 2009	.72017407	.55850089	.92864794
Combined	.73670962	.59009188	.91975689

Supplementary Figure S5 Sensitivity Analysis Results (Diabetic retinopathy progression)

Publication Bias (Diabetic retinopathy progression)

According to Supplementary Figure S6, no publication bias was found.

Tests for Publication Bias

Begg's Test

adj. Kendall's Score (P-Q) = -15
Std. Dev. of Score = 11.18
Number of Studies = 10
z = -1.34
Pr > |z| = 0.180
z = 1.25 (continuity corrected)
Pr > |z| = 0.210 (continuity corrected)

Egger's test

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.0359491	.20188	0.18	0.863	-.429587	.5014852
bias	-1.731583	1.242189	-1.39	0.201	-4.596075	1.132909

Supplementary Figure S6 Egger's and Begg's Test (Diabetic retinopathy progression)

8

Chapter 8

Evaluation design of the Social Engagement Framework for Addressing the Chronic-disease-challenge (SEFAC): a mindfulness-based intervention to promote the self- management of chronic conditions and a healthy lifestyle

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ABSTRACT

Background The Social Engagement Framework for Addressing the Chronic-disease-challenge (SEFAC) project intends to empower citizens at risk of or with type 2 diabetes (T2DM) and/or cardiovascular disease (CVD) to self-manage their chronic conditions through the SEFAC intervention. The intervention combines the concepts of mindfulness, social engagement and information and communication technology support, in order to reduce the burden of citizens with chronic conditions and to increase the sustainability of the health system in four European countries.

Methods A prospective cohort study with a 6-month pre-post design will be conducted in four European countries: Croatia, Italy, the Netherlands and the United Kingdom. A total of 360 community-dwelling citizens ≥ 50 years of age will be recruited; 200 citizens at risk of T2DM and/or CVD in the next ten years (50 participants in each country) and 160 citizens with T2DM and/or CVD (40 participants in each country). Effects of the intervention in terms of self-management, healthy lifestyle behavior, social support, stress, depression, sleep and fatigue, adherence to medications and health-related quality of life will be assessed. In addition, a preliminary cost-effectiveness analysis will be performed from a societal and healthcare perspective.

Discussion The SEFAC project will further elucidate whether the SEFAC intervention is feasible and (cost-) effective among citizens at risk of and suffering from T2DM and/or CVD in different settings.

Trial registration ISRCTN registry number is ISRCTN11248135. Date of registration is 30/08/2018 (*retrospectively registered*).

KEYWORDS Prevention; Self-management; Type 2 diabetes; Cardiovascular disease; Mindfulness; Lifestyle; Social engagement; ICT support

BACKGROUND

Persons with a chronic condition are responsible for the management of their chronic condition everyday.[1] Successful self-management of chronic conditions could help citizens handle their life with independence to some extent despite their medical condition and to feel healthy despite their limitations.[2] Moreover, within the context of the overloaded healthcare and welfare systems, the ability of citizens with a chronic condition to take care of themselves for as long as possible has become increasingly important.[1, 2]

Several concepts have recently been explored as a basis to define the most effective and efficient model to deal with the chronic condition challenge.[3] One of these concepts concerns mindfulness. A review of 15 studies suggested that mindfulness-based stress reduction interventions could help participants with chronic conditions to better cope with symptoms and better achieve overall well-being, quality of life and health outcomes.[4] Some studies indicate that a mindfulness intervention is an effective tool for diabetes as well as chronic low back pain self-management.[5, 6]

A second concept concerns social engagement. Social engagement programmes provide practical support to help citizens achieve aspirations and makes them better connected to their community. One example of a social engagement programme is the Newquay Pathfinder Programme.[7] Important conceptual elements of this programme include shaping services around people and communities, motivating people to achieve their aspirations through a 'guided conversation' and the use of volunteers.[7, 8]

Information and communication technology (ICT) (for instance, a telephone-based interactive system or an application on smartphone) is the third concept which is considered as an important enabler of self-management partnership.[1] This means that people with chronic conditions can self-manage their health using ICT and health professionals are consulted to support them in this role.[1, 9, 10] Previous studies indicate that ICT support improves the self-management of citizens with chronic conditions.[11, 12]

Numerous studies have demonstrated the effectiveness of self-management programmes.[13-15] However, most studies have focused on a specific concept and/or a specific chronic condition.[16] Furthermore, cross country comparisons of the effectiveness of these programmes is recommended as well as cost-efficiency data regarding these self-management programme.[17]

THE SEFAC PROJECT

The Social Engagement Framework for Addressing the Chronic-disease-challenge (SEFAC) project was set up to respond to the call of the Third EU Health Programme (2014-2020; PJ-04-2016: Support to Member States and stakeholders to address the chronic disease challenge; http://sefacproject.eu). The aim of the SEFAC project is to empower citizens ≥ 50

years of age at risk of or with type 2 diabetes (T2DM) and/or cardiovascular disease (CVD) to self-manage their chronic conditions through the SEFAC intervention which combines the concepts of mindfulness, social engagement as well as ICT support. Furthermore, the project will evaluate (cost) effectiveness, which will provide insight in costs of potential policies contributing to the prevention of chronic conditions. In this project, study sites in four European countries will implement the SEFAC intervention: Rijeka in Croatia, Treviso in Italy, Rotterdam in the Netherlands and Camborne in the United Kingdom.

Objectives

The main objective of this paper is to evaluate the SEFAC intervention in terms of benefits for the target population (citizens ≥ 50 years of age at risk of or with T2DM and/or CVD). The following research questions will be answered:

1. What are the effects of the SEFAC intervention for participants in terms of self-management, healthy lifestyle behavior, social support, stress, depression, sleep and fatigue, adherence to medications and health-related quality of life (HRQoL)?
2. What are the societal cost savings of the SEFAC intervention in terms of reducing healthcare utilization and productivity losses among the target population?
3. To what extent is the target population satisfied with the SEFAC intervention as a whole and with its three specific elements (mindfulness, social engagement and ICT support)?

Study hypotheses

Our hypothesis is that the SEFAC intervention improves the self-management skills of participants, promotes more favorable lifestyle behaviors, improved social support, reduce participants' stress, depression, sleeping problems and fatigue and improve participants' adherence to medication and HRQoL at six month of follow-up compared to baseline. In addition, we hypothesize that society will benefit from the intervention through to a reduced use of healthcare resources and greater productivity. Finally, we hypothesize to reach a satisfaction score of 7 or higher on a 1-10 scale for the SEFAC intervention as a whole, with higher scores representing greater satisfaction.

METHODS/DESIGN

The SEFAC intervention

The SEFAC intervention was designed and developed by partners of the SEFAC project and includes the concepts of mindfulness, social engagement as well as ICT support (figure 1), which are offered to participants in parallel.

Mindfulness training is offered in a series of 3 to 7 workshops, 2,5 hours each, which will be held once a week for 3 to 7 weeks. Every training will be led by trained mindfulness professionals. The training includes three 'obligatory' workshops on training mind and body for health and wellbeing, healthy habits and a healthy mindset as well as four voluntary

workshops on healthy eating, healthy physical activity, healthy relationships and healthy life with chronic conditions. The number of participants per training will be no more than 30. Over the workshops, participants will learn to foster greater awareness of present moment experience to help them better manage life's ups and downs, support a healthy lifestyle and enhance the quality of daily life.

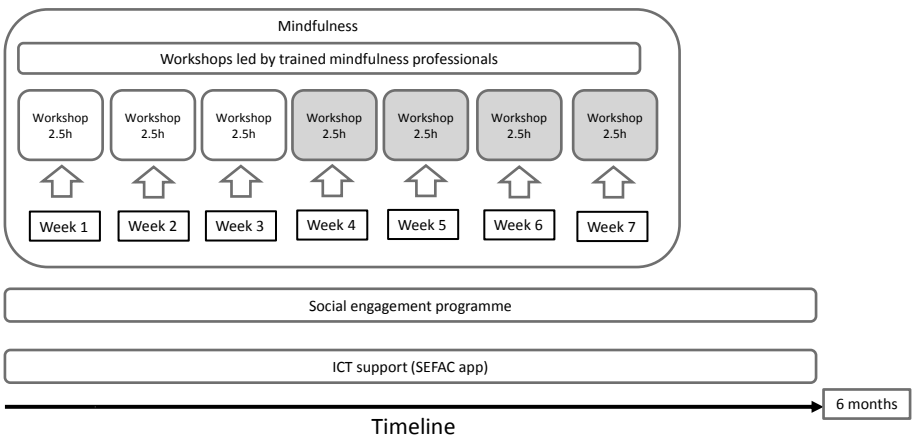

Figure 1 The SEFAC intervention

In parallel to the mindfulness training, participants are invited to enroll in the social engagement programme of the SEFAC project which is based on the Newquay Pathfinder Programme.[7] The precise role of the volunteers may differ depending on the geographical, cultural and social context of the four study sites. At least, volunteers help citizens identify ways to build self-confidence and self-reliance through guided conversations.[7] In addition, they may support to the mindfulness training and provide practical help in adopting major lifestyle changes and in getting better connected to their community.

Finally, participants will be invited to download the free SEFAC app on their mobile phone and use it as ICT support for six months, starting from the first workshop. The SEFAC app is a multi-modular tool that has been developed for the android operating system. The app aims to support change of lifestyle behaviors among people with and without chronic diseases, according to the stage of change the individual is in at a particular point in time. Participants are encouraged to engage in the practices, lessons, tips and reflections offered through the app (see Supplementary Figure 1).

Study design, setting and procedures

A prospective cohort study with a 6-month pre-post design will be conducted.[18] Six-month follow-up data of participants will be compared with the same participants' baseline data. The study protocol has been reviewed by the Ethical Review Boards at the study sites in Rijeka, Treviso, and Rotterdam; at the study site in Camborne, the decision tool of the NHS Health Research Authority was applied in accordance with the applicable regulations in the

UK. See Declaration section. In all cases, written informed consent is obtained before participants enter the study.

In each study site, we will recruit community-dwelling citizens over 50 years old using different strategies taking the capacity, organizational and environmental characteristics of the 4 study sites in consideration, as described below.

Rijeka is a port city in the Republic of Croatia with a population of 128,384.[19] Participants will be recruited from public health events where free health checks are provided, including measurement of blood pressure and blood glucose, as well as through free community exercise programmes. Interested citizens can talk about the risk of developing T2DM and/or CVD with a health professional. Eligible citizens are informed about the SEFAC project and are invited to provide written informed consent and to participate in the study.

Treviso is a city in the Veneto region in northeast Italy with 84,954 inhabitants.[20] Participants will be recruited from open events and through announcements on health-related social network platforms. Interested citizens can talk face-to-face with health professionals about the risk of developing T2DM and/or CVD, and can be suggested to visit their general practitioner (GP). Eligible citizens are informed about the SEFAC project and are invited to provide written informed consent and to participate in the study.

Rotterdam is a port city in the Netherlands with a population of 638,714.[21] Participants will be recruited from open community events and public announcements. Citizens are informed about the SEFAC project in-person and/or via the SEFAC website. Interested citizens can express their interest to participate online, by e-mail and in a conversation with a health professional, face-to-face or by telephone. Eligible citizens are invited by the research team to provide written informed consent and to participate in the study.

Camborne is a town in South West England with a population of 20,436.[22] Participants will be recruited by informing and inviting visitors of the Veor Surgery, a general practitioner practice. Recruitment will also take place through open events. Eligible participants will receive information about the SEFAC project and are invited to provide written informed consent and to participate.

Study population and eligibility to participate in the study

We aim to include 360 participants in total (90 participants in each study site). The target population consists of community-dwelling citizens ≥ 50 years of age, of which 200 participants at risk of T2DM and/or CVD in the next ten years (50 participants in each study site) and 160 participants with T2DM and/or CVD (40 participants in each study site). Citizens are not eligible to participate when they are diagnosed with mild or serious cognitive impairment, terminally ill or scheduled to enter secondary or tertiary care settings for a long period of time, lacked the basic knowledge of the local language or when they are not able to make an informed decision regarding participation in the study.

Data collection

Data will be collected from participants before the start of the first workshop (baseline, T0) and at 6 months (T1) with the use of a questionnaire. The instruments used for the outcome measures are described in measurements section. The instruments or items without validated translations are translated by translators. The study team discussed the translations and adapted the translation when needed.

Measurements

Our objective is to evaluate the effects of the SEFAC intervention on self-management, healthy lifestyle behavior, social support, stress, depression, sleep and fatigue, adherence to medications and HRQoL. Self-management is measured with General Self-efficacy Scale (GES)[23] as well as the short 6-item version of the Chronic Disease Self-Efficacy instrument (CDSE-6)[24] which measure the confidence in one's ability to deal with health problems. The CDSE-6 covers domains that are common across many chronic conditions, such as symptom control, role function, emotional functioning and communicating with physicians.

With respect to healthy lifestyle behavior, we will assess physical activity, healthy eating, sedentary behavior, smoking and alcohol use. Physical activity is measured with six items on physical exercise[24] and five items of The Physical Exercise Self-Efficacy Scale (PESES)[25]. Healthy eating is measured with three items on the intake of fruits, vegetables and breakfast and five items of The Nutrition Self-Efficacy Scale (NSES)[26]. Sedentary behavior is measured with one item from the International Physical Activity Questionnaire (IPAQ)[27], current smoking is assessed with a single yes/no question and the frequency of alcohol use is determined with one item from the AUDIT-C[28].

Social support is measured with the 3-item Oslo Social Support scale (OSS-3), regarding the primary support group, interest and concern shown by others and ease of obtaining practical help[29]. Stress is measured with the 10-item Perceived Stress Scale (PSS-10)[30]. Depression is measured with the 8-item Patient Health Questionnaire depression scale (PHQ-8)[31]. Sleep and fatigue are measured by visual analog scales, ranging from 0 (no sleeping problem/fatigue) to 10 (severe sleeping problem/fatigue).

Adherence to medication is measured with six items from the Short Medication Adherence Questionnaire (SMAQ)[32], a short tool based on questions posed directly to the participant regarding his/her medication-taking habits.

HRQoL is measured with the 12-item Short-Form health survey (SF-12)[33] and the EuroQol- 5 Dimensions- 5 level (EQ-5D-5L)[34] instrument. The SF-12 is a patient-reported survey which includes both a physical dimension (physical functioning, role-physical, pain and general health) and a mental dimension (vitality, social functioning, role-emotional and mental health). SF-12 scores can be summarized in the Physical Component Summary (PCS) and the Mental Component Summary (MCS), ranging from 0 (worst) to 100 (best quality of life).[33] The EQ-5D-5L is often used in the Quality-Adjusted Life Year calculation to determine the cost-effectiveness of an intervention. It has five dimensions: mobility, self-care, activity, pain

and anxiety. Each dimension has five levels, ranging from no problems (level 1) to serious problems (level 5). Hence, the EQ-5D-5L has 3,125 possible health states. Utility values for these health states are available for the study sites of each participating country.[34] As part of the EQ-5D-5L, participants are also asked to indicate their experienced current health state on a visual analog scale, 0 being the worst imaginable health and 100 being the best imaginable health.

Additionally, we will evaluate healthcare utilization and productivity losses. Healthcare utilization is measured with four questions from the Self-Management Resource Center (SMRC) Health Care Utilization questionnaire regarding doctor appointments, the use of hospital emergency rooms and hospital admissions.[35, 36] Productivity losses are measured with two domains from the Productivity Costs Questionnaire (PCQ)[37]: lost productivity at paid work due to absenteeism (6 items) and lost productivity at unpaid work (3 items).

Socio-demographic characteristics include age, gender, country of birth, marital status, household composition, education level, employment situation and health conditions. There is an open box at the end of the questionnaire for any additional remarks.

The follow-up questionnaire at 6 months (T1) will be identical to the baseline questions except for the addition of questions on the satisfaction of the target population with the intervention. In the T1-questionnaire, we will add 6 items to rate the satisfaction with the whole SEFAC intervention as well as specific concepts (mindfulness, social engagement and ICT support) on a scale from 1 to 10.

Power considerations

The power considerations are conducted according to the methods of a previous study.[38] We will include net 113 participants at T0 in each study site (4 study sites * 113 = 452 study participants). When the loss to follow-up between T0 and T1 will be 20%, we will have complete data of 360 participants at T1. Assuming equal standard deviations (SD) at T0 and T1, an alpha of 0.05 and power of 0.80, and taking into account the cluster design (4 participating study sites) with an average cluster size of 90 participants (360/4) and an intra-class correlation coefficient of 0.02, a difference of 0.24 SD between T0 and T1 can be established regarding the continuous outcome measures for this expected sample size and under these conditions. For instance, regarding HRQoL as measured by the SF-12, a difference of 2.74 points can be established between T0 and T1 for the PCS (SD = 11.4) and 2.86 points for the MCS (SD = 11.9).[39]

Statistical analysis

Descriptive statistics will describe characteristics of participants in the total study population and in each study site. In order to evaluate differences between T0 and T1 measurements, multiple linear regression analyses (for continuous outcome variables) and multiple logistic regression analyses (for dichotomous variables) will be adopted in the total study population. In addition, the analyses will be done for each study site separately, and possibly

other subgroups analyses will be performed through formal interaction tests for variables that will likely effect the intervention itself, such as age, gender and education level.

A preliminary cost-effectiveness analysis will be performed with the baseline measurement as control group from a societal and healthcare perspective. Healthcare costs for individual participants will be determined by multiplying resource use with corresponding unit prices for 2017, including doctor appointments, hospital emergency rooms and hospital admissions. Productivity losses for individual participants (lost productivity at paid work due to absenteeism and lost productivity at unpaid work) will follow from the PCQ. Utility values will be obtained through the EQ-5D-5L instrument.

Dissemination

An Advisory Board with experts from five countries (China, Croatia, Finland, the Netherlands and Sweden) has been set up. The Advisory Board will provide critical suggestions and comments throughout the project. The project team will disseminate the scientific project results through publications in scientific peer-reviewed journals and conferences. We adopt the project website (http://sefacproject.eu/) to further disseminate the key findings of our project to all stakeholders. The European Local Inclusion and Social Action Network (ELISAN) will disseminate the project results through social media.

DISCUSSION

This paper describes the design of a prospective cohort study which aims to evaluate the effects of the SEFAC intervention for citizens at risk of or with T2DM and/or CVD on self-management, healthy lifestyle behaviors, social support, stress, depression, sleep and fatigue, adherence to medications and HRQoL as well as the (cost-) effectiveness of the SEFAC intervention.

Strengths of the study are that, to our knowledge, this study is the first to develop and implement an intervention combining the concepts of mindfulness, social engagement and ICT support in Europe. Our study may provide evidences on the generalizability of the intervention in different European countries through recruiting the target population in different settings. Additionally, the SEFAC project will provide information on cost-effectiveness of self-management programmes to fulfill the gap of limited data in this area.

The study also has some limitations and challenges. Firstly, recruiting citizens at risk of or with T2DM and/or CVD may be a challenge. In order to increase the participation rates, open events aimed at recruiting participants will be held according to the capacity, organizational and environmental characteristics of the 4 study sites. Secondly, it was not practicable to include a control group. To ensure that a citizen would not feel excluded, we prefer to offer the intervention to all citizens that meet our criteria. Instead, we apply a 6-month pre-post design, using the baseline measurement as the 'control group'. Thirdly, we will try to capture the most important confounding factors in our questionnaire. However, it is still possible that we miss relevant variables.

Chronic diseases are the main cause of morbidity and mortality in Europe and due to their social impact and economic implications, their prevention and management are important challenges in realizing the sustainability of health systems in Europe. By combining mindfulness training, social engagement and ICT support, we expect the SEFAC intervention to be a feasible and cost-effective programme to promote self-management and self-care of citizens at risk of and suffering from chronic diseases.

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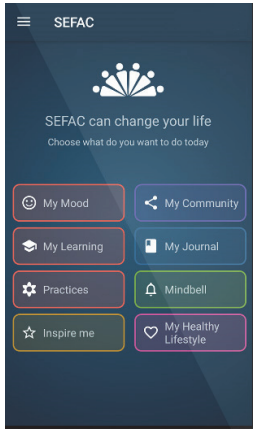
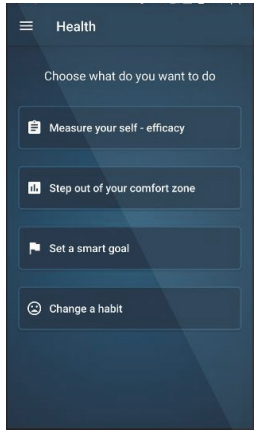
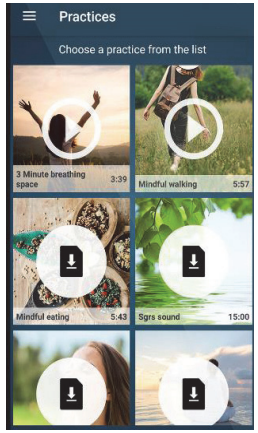


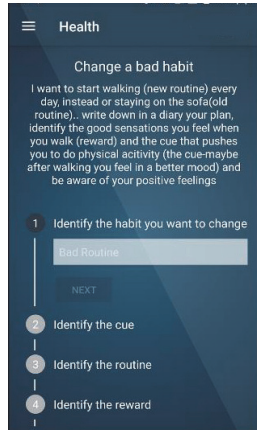
Supplementary Figure 1 Screen capture of SEFAC app: part 1



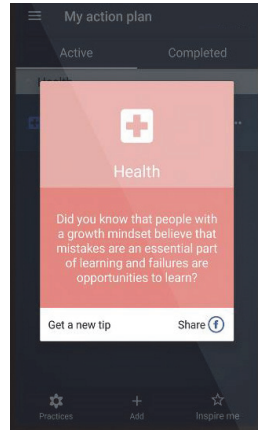
Supplementary Figure 2 Screen capture of SEFAC app: part 2



Supplementary Figure 3 Screen capture of SEFAC app: part 3



Supplementary Figure 4 Screen capture of SEFAC app: part 4



Supplementary Figure 5 Screen capture of SEFAC app: part 5

9

Chapter 9

General Discussion

The aim of this thesis was to study health promotion for frailty as well as chronic conditions. Following the public health framework, we: (1) defined problems (surveillance), (2) identified the cause or risk and protective factors for the problems, (3) determined how to prevent or control the problems and (4) implemented effective interventions and evaluated their effect.

In this thesis, we aim to answer the following research questions:

1. What are the associations between physical, psychological and social frailty and health-related quality of life (HRQoL) among community-dwelling older adults? **(Step 1 of Public Health Framework)**
2. What are the longitudinal associations between physical activity and frailty as well as the association between a 12-month change in physical activity and frailty among community-dwelling older adults? **(Step 2 of Public Health Framework)**
3. What are the reliability and validity of the Tilburg Frailty Indicator (TFI) in five European countries? **(Step 3 of Public Health Framework)**
4. How does the Urban Health Centres Europe (UHCE) approach perform in terms of specific process components? **(Step 3 of Public Health Framework)**
5. What are the effects of peer support on glycemic control for adults with type 2 diabetes (T2DM) and the characteristics of effective peer support? **(Step 3 of Public Health Framework)**
6. What are the effects of interventions targeting modifiable risk factors on diabetic retinopathy (DR) for adults with T2DM and the characteristics of effective interventions? **(Step 3 of Public Health Framework)**
7. Could the Social Engagement Framework for Addressing the Chronic-disease-challenge (SEFAC) intervention be effective to promote the self-management of chronic conditions and a healthy lifestyle? **(Step 4 of Public Health Framework)**

In this chapter, the main findings of the studies reported in this thesis will be discussed (9.1). The methodological issues that could have affected the findings will be addressed (9.2). Finally, recommendations for future research, policy and practice will be outlined (9.3).

9.1 MAIN FINDINGS AND INTERPRETATION

Health promotion for people with frailty

The first step of the public health framework is to define the problem. Frailty is a major health condition associated with ageing.[1] Improvement of health and quality of life is an objective of health promotion.[2] Therefore, understanding the association between frailty and health-related quality of life (HRQoL) among older adults could help us identify the problem and could provide insight needed for further development of effective interventions to improve HRQoL (See Figure 9.1.1). However, studies on the association between frailty and HRQoL are relatively scarce and show contradicting results. In **Chapter 2**, the association between frailty and HRQoL were studied. The results show that frailty had a negative association with both physical and mental HRQoL. This is in line with previous studies reporting that frail people have a poorer physical and mental HRQoL than not frail people.[3-7] We also analyzed the

associations between the subdomains of frailty and HRQoL. The results show that physical frailty had the strongest association with physical HRQoL, and psychological frailty had the strongest association with mental HRQoL. The associations between social frailty and both physical and mental HRQoL were significant when controlling for physical and psychological frailty, which was not reported by previous studies. Our results confirm the importance of considering the three domains of frailty to improve HRQoL among frail older adults. So, the study confirmed that frailty is an issue among older adults that has a negative association with both physical and mental HRQoL.

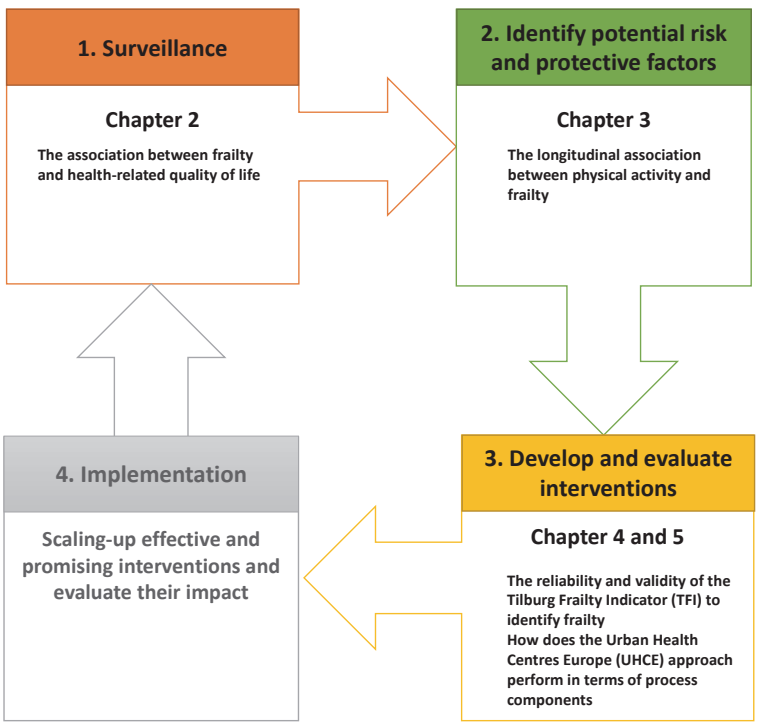


Figure 9.1.1 Public Health Framework: the steps of public health approaches of studies on health promotion for frailty (Chapter 2-5)

*This is an adaptation of an original work "The public health approach. Geneva: World Health Organization (WHO); 2010. Licence: CC BY-NC-SA 3.0 IGO". This adaptation was not created by WHO. WHO is not responsible for the content or accuracy of this adaptation. The original edition shall be the binding and authentic edition.

The second step of the public health framework is to identify the risk and protective factors for health issues. Maintaining a healthy lifestyle in older age is suggested to be a protective factor for a lower level of frailty.[8-11] The indicators of a healthy or unhealthy lifestyle often refer to lifestyle behaviors, such as eating habits, physical activity and sedentary behaviors, tobacco and alcohol consumption.[12] Physical activity levels tend to decline with age.[11] Older adults may experience multiple barriers for physical activity, such as specific health conditions,

poor balance, muscle weakness, shortness of breath and fear for falling.[13] Studies on the association between physical activity and frailty among older adults show contradictory results. Moreover, most of the longitudinal studies on physical activity and frailty examine baseline physical activity only in relation to changes in frailty[14, 15], and studies on the association between change in physical activity and frailty are relatively limited. Therefore, we studied the longitudinal association between frequency of moderate physical activity and frailty as well as the association between a 12-month change in frequency of moderate physical activity and frailty in **Chapter 3** (See Figure 9.1.1). Our results show that both maintaining a regular frequency of physical activity and increasing to a regular frequency of physical activity were associated with maintaining or improving the level of frailty among older adults, not only in the physical domain, but also in the psychological and social domains of frailty. In summary, the result support that maintaining a regular frequency of physical activity and (if not present) increasing to a regular frequency of physical activity could be a protective factor with regard to frailty.

The third step of the public health framework is to determine how to prevent or control the problems. Frailty status might be reversible with the implementation of specific interventions.[16-18] Therefore, to identify frail people has been proposed as a step for better management and control of frailty.[19] The Tilburg Frailty Indicator (TFI) is a short self-reported questionnaire including 15 items addressing 3 domains: the physical, psychological and social domains.[20] However, research on the properties of the TFI is relatively limited.[21] For example, the TFI has not yet been validated in Greece, Croatia or the United Kingdom (UK). Evaluation of the TFI in several countries could help us to determine whether it works well in studying frailty in various populations (See Figure 9.1.1). In **Chapter 4**, we assessed the reliability and validity of the full TFI and its three domains in a population of community-dwelling older adults from 5 European countries, including Spain, Greece, Croatia, the Netherlands and the UK. In addition, the reliability and validity were assessed for each country separately. Our results support the reliability and validity of the TFI. So, the TFI may be applied as an instrument to measure frailty in community-dwelling older adults for large-scale population studies on frailty in the five European countries.

For the third step of public health framework, it is also important to evaluate the process components of the interventions to increase the understanding of underlying reasons for why some works while another do not (See Figure 9.1.1). In **Chapter 5**, we evaluated the process components of the implementation of the Urban Health Centres Europe (UHCE) approach using the Steckler and Linnan framework[22, 23], including reach of the target population, dose of the intervention actually delivered to and received by participants, and satisfaction of main stakeholders with the intervention. The UHCE approach was a preventive coordinated care approach aimed at promoting healthy ageing by decreasing falls, polypharmacy, loneliness and frailty among community-dwelling older adults.[24] The UHCE approach shows promising, but small positive effects in tackling recurrent falls and frailty;[25] the study shows that there may be barriers that hinder person's engagement in care. Our results show that people in

poor health might have enrolled less often. Care activities that require transport or a higher level of activity might not reach older adults who are limited in their functioning. So, it may be important to pay more attention to special groups of older adults, such as people in poor health condition or who are limited in functioning, when we develop further interventions on frailty.

Health promotion for chronic conditions

The first two steps of public health approach on chronic conditons have been studied thoroughly by previous studies. Diabetes is a chronic condition with significant morbidity and mortality, and over 90% patients with diabetes have type 2 diabetes (T2DM).[26] Due to the heavy burden caused by diabetes in affected individuals, families and societies in general, diabetes has been identified as a major public health problem for several decades.[27] The risk factors for diabetes can be divided into two categories: modifiable (can be changed) and non-modifiable (cannot be changed) factors.[28] Non-modifiable factors include a person's family history, age, gender, racial/ethnic and socioeconomic status.[29, 30] Modifiable factors that increase the risk of developing diabetes, particularly T2DM, include hyperglycemia, hypertension, hyperlipidemia, obesity, and unhealthy lifestyle.[29, 30]

The third step of the public health framework is to determine how to prevent or control the problems. On-going changes in lifestyle including losing weight, increasing physical activity, eating healthy foods, medication management and monitoring clinical and metabolic parameters have been shown to be effective in better management and control of diabetes as well as its complications, especially for T2DM.[30-32] However, these changes in lifestyle are difficult for the adults with T2DM due to the requirement of strong self-management or self-regulation skills.[31, 33] Peer support, a kind of ongoing support from nonprofessionals, may effectively provide ongoing self-management support.[31] Therefore, we evaluated the existing peer support interventions and compared their effects to find out what works better in management of T2DM (see Figure 9.1.2). In **Chapter 6**, the effects of peer support on glycemic control for patients with T2DM and the important characteristics among providers, types, intervention duration and effect duration were studied through meta-analysis among relevant randomized control trials (RCTs). Peer support was found to achieve modest but statistically significant benefits on glycemic control for patients with T2DM. Peer support provided by patients themselves as a group or provided by nonprofessionals like community workers may have significantly better effect. Duration >3 and ≤6 months is more likely effective and the effect of peer support on glycemic control weakens over time especially after the end of intervention, which points to the importance of ongoing support.[34] According to the results of our study, Curriculum-combined-reinforcement-intervention and Home-visit-intervention were suggested, and peer support duration with the best metabolic effectiveness was >3 and ≤6 months.

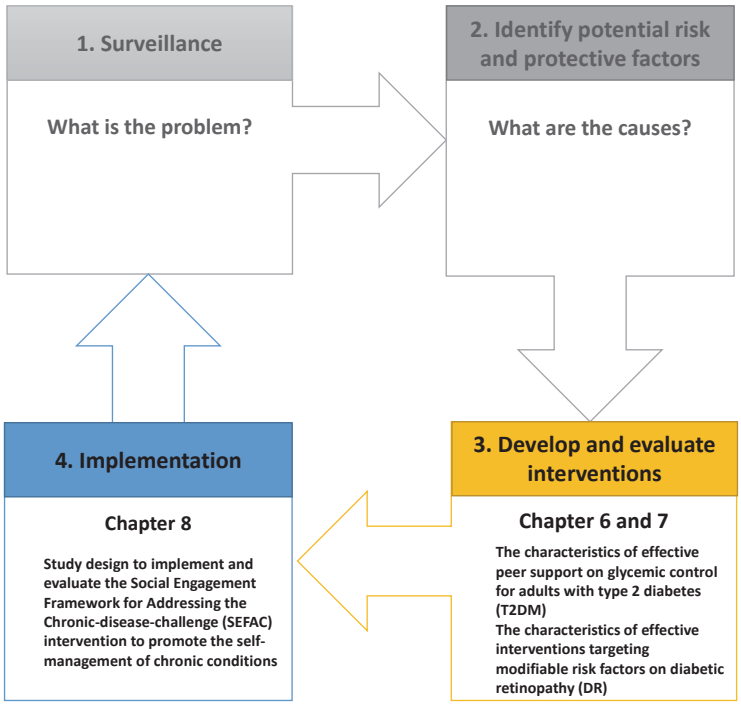


Figure 9.1.2 Public Health Framework: the steps of public health approaches of studies on health promotion for chronic conditions (Chapter 6-8)

*This is an adaptation of an original work "The public health approach. Geneva: World Health Organization (WHO); 2010. Licence: CC BY-NC-SA 3.0 IGO". This adaptation was not created by WHO. WHO is not responsible for the content or accuracy of this adaptation. The original edition shall be the binding and authentic edition.

Increase of the prevalence of diabetes has led to increase in related complications in the population.[35] Diabetic retinopathy (DR), a complication of diabetes, is an important cause of preventable blindness.[36] Following the third step of public health framework, we evaluated the existing studies on interventions targeting modifiable risk factors and compared their effects to find out what works better to prevent and control DR among patients with T2DM (see Figure 9.1.2). In **Chapter 7**, the effects of interventions targeting modifiable risk factors of DR (blood glucose, blood pressure, lipid, dietary, physical activity and smoking) on reducing the risk of developing DR and/or its worsening as well as the important characteristics of effective interventions are studied through a meta-analysis of relevant RCTs. Interventions targeting modifiable risk factors of DR were found to be effective in reducing the risk of developing DR and DR worsening. Multifactorial interventions with individualized targets and communication between health professionals and patients were more effective than other interventions in the prevention and control of DR. According to these findings, multifactorial interventions with individualized target and communication may be recommended to prevent and control DR.

The fourth step of public health framework is to implement effective interventions and to evaluate their effect. The Social Engagement Framework for Addressing the Chronic-disease-challenge (SEFAC) project intends to empower citizens at risk of or with T2DM and/or cardiovascular disease (CVD) to self-manage their chronic conditions through the SEFAC intervention. Following the fourth step of the public health approaches, we described the design of a prospective cohort study, which aims to evaluate the effects of the SEFAC intervention in **Chapter 8** (see Figure 9.1.2). The SEFAC intervention combines the concepts of mindfulness, social engagement and information and communication technology support (ICT), in order to reduce the burden of citizens with chronic conditions and to increase the sustainability of the health system in four European countries. The project aims to study the effects of the SEFAC intervention on self-management, healthy lifestyle behaviors, social support, stress, depression, sleep and fatigue, adherence to medications and HRQoL. There is also attention for the (cost-) effectiveness of the SEFAC intervention. The study aims to provide insight regarding the feasibility and effects of the intervention in different European countries and different settings.

9.2 METHODOLOGICAL CONSIDERATIONS

The results of this thesis should be viewed in the light of some methodological considerations. Specific methodological considerations have been discussed for the studies in this thesis. In the following paragraphs some general methodological considerations will be described, related to the study design, study population, measurements and statistical analysis.

Study design

Chapters 2-5 in this thesis used data from UHCE project, which is a controlled trial implemented in community settings at study sites in five European countries. Participants in the intervention group received care in accordance with the UHCE approach. In **Chapter 2**, a cross-sectional study with the baseline data of the UHCE project was conducted to study the association between frailty and HRQoL. However, the cross-sectional design of this study did not allow for the assessment of a potential causal relationship between frailty and HRQoL. In **Chapter 3**, a longitudinal design was used to study the association between physical activity and frailty. Participants in both the intervention and control group were included in the analyses. The UHCE approach may have led to improvement in health which could result in the over-estimation of the effect of physical activity on frailty. Therefore, being in the intervention condition (or not) was a factor for which we adjusted the analyses regarding the association between physical activity and frailty; this was done by adding it to the regression models as a covariate. We also repeated the analyses for the control group only and found similar results. Additionally, we considered the results of those persons who had received specific UHCE approach may have had an effect on the changes in the frequency of physical activity. Therefore, we conducted a sensitivity analysis to control for specific UHCE interventions that may promote physical activity and found similar results. This study (Chapter 3) was an observational study, and therefore causality between physical activity and

frailty cannot be inferred. In **Chapter 5**, the process components of the UHCE approach implementation were evaluated using the Steckler and Linnan framework. One reason to develop the process evaluation was to explain why certain effects were found in the effect evaluation that was published previously and pinpoint to components of interventions that were effective.[22] However, the complex interventions may include the interplay of multiple components. In **Chapter 6-7**, the design and conduct of RCTs could affect the meta-analyses. For example, the non-blinding of trial treatment may lead to biased assessment of some outcomes.[37] None of the RCTs included in the meta-analyses was a double-blinded study, with the exception of one RCT in Chapter 6. In **Chapter 8**, we proposed an evaluation design for the Social Engagement Framework for Addressing the Chronic-disease-challenge (SEFAC) project. We suggested to apply a 6-month pre-post design, using the baseline measurement as the 'control group'. However, this pre-post design is relatively weak in terms of internal validity, because it does not eliminate the possibility that the posttest results might have occurred regardless of the intervention.[38]

Study population

All studies in this thesis, with the exception of Chapter 6 and 7, relatively healthier participants may have enrolled into the studies which potentially caused selection bias. In **Chapter 5**, we used qualitative data from focus groups with older persons and professionals. Older persons included in the focus groups might have been those who were most positive about the UHCE. Additionally, there were relatively many missing data for questions on satisfaction of the UHCE approach. Participants who did not reply to these questions could have thought these questions were not applicable to them or were the people who were less involved.

Measurements

In all studies of this thesis, people from different countries were included, and cultural differences in the interpretation of questions might have caused some variation between countries.

Most data collected in all the studies, with the exception of Chapter 6 and 7, were based on self-reported questionnaires which could have led to response bias to some extent. For example, participants may have been tempted to provide socially desirable responses.[39] Furthermore, participants may report inaccurate data because they cannot remember or omit details, such as the frequency of alcohol use, smoking and physical activity. This problem, known as recall bias, is a potential weakness in studies that use self-reporting.[40]

Frailty was measured by the TFI in Chapter 2-5. In **Chapter 2**, cut points of frailty and its three domains of the TFI were applied to explore the association between frailty and HRQoL (compared to using continuous scores), which might cause information loss. However, we performed analyses on the association between continuous frailty scores and HRQoL and found similar results. In **Chapter 4**, the socio-cultural and language differences in the interpretation of individual items of the TFI between countries were not assessed. Most of the alternative measures chosen to examine convergent and divergent validity and

concurrent validity have been widely applied by previous studies. However, there is no 'golden standard' of frailty to be used as alternative measure of the TFI. The alternative measures for psychological and social domains was limited by the available data in the UHCE project.

In **Chapter 3**, physical activity was measured by one question, instead of a validated multi-item instrument such as the International Physical Activity Questionnaire (IPAQ)[41]. The item that we applied could not differentiate between type of activity and does not take the duration of activity into account. However, some previous studies[42-44] indicate that using a single question to measure physical activity is appropriate in certain circumstances, e.g. when the sample size is large, when more complex methods would add to respondent burden, and when collecting data from a broad range of settings. Grill et al. (2012) also suggest that the reliability and validity of a single question to briefly classify physical activity levels is acceptable.[45] Secondly, we transferred the ordinal variable of physical activity into a dichotomous one; however, we conducted additional analyses on the association between physical activity and frailty with the ordinal variable of physical activity and found similar results. Lastly, there may be overlap between physical activity and two items of the TFI (walking and balance) which could cause over-estimation of the association. However, when we explored the association between physical activity and overall frailty, after deleting these two items the results were similar.

Statistical analysis

Confounding and moderation

Confounding variables are associated with both the determinant and the outcome under study, but are not on the causal pathway.[46] Ignoring confounding variables could lead to an overestimation or underestimation of the true association between the determinant and the outcome.[46] In all studies in this thesis, with the exception of Chapter 4, 6 and 7, we adjusted for potential confounders, which were carefully chosen based on previous literature, availability in the data and exploratory analyses. However, the possibility of residual confounding due to unmeasured or insufficiently measured determinants cannot be ruled out.

'Moderation' happens when the association between the determinant and the outcome varies according to a third variable.[47] In **Chapter 2, 3 and 8**, we tested moderation by formal interaction tests and stratified data when there was significant interaction. We applied the Bonferroni corrections for interaction testing in case of multiple testing to avoid 'chance findings'.

Meta-analysis (Chapter 6 and Chapter 7)

"Any kind of variability among studies in a meta-analysis may be termed heterogeneity".[48] Clinical heterogeneity includes variability in the participants, interventions and outcomes, and methodological heterogeneity includes variability in study design and risk of bias.[48] Variability in the intervention effects being evaluated in the meta-analysis is known as statistical heterogeneity, and is a consequence of clinical or methodological heterogeneity, or both,

among the studies.[48] This statistical heterogeneity can be quantified, but there is usually "uncertainty about the clinical sources of this heterogeneity and how important the differences really are".[49] Subgroup analyses could be adopted to explore the heterogeneity in the meta-analysis.[48] In **Chapter 6 and 7,** heterogeneity was moderate to high across the studies included in the meta-analyses. Subgroup analyses were only partly able to explain this variation. A high level of heterogeneity was still observed in some subgroups. Further studies are needed to confirm our findings in some subgroups with high heterogeneity.

Clinical meaning of (changes of) the TFI scores
In **Chapter 3**, statistically significant differences in frailty scores between baseline and follow-up were found. Future studies should explore what changes of the TFI scores correspond to clinically meaningful changes regarding the level of frailty.[50, 51]

9.3 RECOMMENDATIONS FOR FUTURE RESEARCH

Frailty
We recommend further studies on the effect of the frequency and intensity levels of PA in order to determine the optimum level of PA required to prevent the progression of physical, psychological and social frailty among older adults.

Our findings indicated that the TFI can be applied as an instrument to study frailty in community-dwelling older adults. We propose to study whether (and how) application of the TFI can be applied in community medicine to identify high risk groups and to promote health. The application of the TFI in health care practice will benefit from the establishment of general population norms or reference scores.[52] Also, the use of the TFI in other settings such as the hospital setting to identify high risk groups and to promote health is recommended.

Previous studies suggested targeting modifiable risk factors at midlife might reduce the occurrence of frailty at later ages.[53] [54] Therefore, we suggest future research on the development and evaluation of interventions that target people at an earlier age.

Chronic conditions
Our results showed that peer support can be effective regarding glycemic control for patients with T2DM. We recommend further studies to verify the results of our subgroup analyses (e.g. Telephone-dominant-intervention and Home-visit-intervention). Peer support is complex and could be influenced by many factors like culture, psychology, emotion and social environment. Therefore, we suggest further research to take these contextual factors into consideration.

As our study was the first to report variation among different types and different follow-up intervals of interventions targeting modifiable risk factors of diabetic retinopathy, we suggest replication studies to confirm our findings. We also recommend more studies on the effectiveness of interventions targeting various modifiable risk factors in prevention and control of diabetic retinopathy.

We suggest effectiveness evaluation of interventions on management of chronic conditions to have a stronger focus on intervention processes and qualitative measures besides quantitative measures. Reporting of details of intervention elements could increase the understanding on the effect of interventions and provide evidence for future development of guidelines of effective interventions.

Healthy ageing

We recommend further studies on integration of health promotion and advancements in the field of smart design and technology, such as ICT and artificial intelligence (AI)[55], to promote active and social lifestyle not only in older population but also in younger ages, which may result in promotion of healthy aging.

9.4 IMPLICATIONS FOR PRACTICE AND POLICY

Health promotion for people with frailty

The associations between social frailty and both physical and mental HRQoL remain significant when controlling for physical and psychological frailty, which supports the potential importance of improving social support or social contact to improve HRQoL. Increasing social contact and social support were associated with better health behavior and HRQoL.[56, 57] In frail people, in addition to (tailored) physical training, increasing social contact or social support to reduce social frailty could be applied to positively influence HRQoL.[58] We recommend health professionals and policy makers to pay more attention to social frailty and consider strategies to improve social support or social contact among older adults.

Both maintaining a regular frequency of physical activity and increasing to a regular frequency of physical activity are associated with maintaining or improving the level of physical, psychological and social frailty among older adults over 70, which supports the relevance of strategies to encourage older adults to maintain physically active. Physical activity interventions could be a promising strategy to promote an active lifestyle among older adults. However, participation in physical activity programs is often low among older adults.[59] Therefore, we suggest to develop strategies to improve participation.

Coordinated preventive care approaches for older adults should address health constraints and barriers that hinder their engagement in care. The study results illustrate the importance of building a trusted relationship of professionals with their older clients; and the importance of a focus on psychosocial barriers for appropriate care use. In addition, the results support the importance of integration of new (effective) preventive approaches in existing health care. The integration may improve the sustainability of the effective approach and make the results of the scientific research into practice. Indeed, in our study, both participants and professionals mentioned they wished activities would continue beyond the project. Therefore, we recommend to develop strategies to enable sustainability of new (effective) prevention approaches.

Health promotion for people with chronic conditions

The results of our study support the relevance of peer support programs for diabetes management. We recommend to support and extend ongoing peer support provided by adults with chronic conditions themselves or by nonprofessionals. We suggest to develop strategies to encourage adults with chronic conditions to participate in peer support programs.

The results of our study show that multifactorial interventions can reduce the risk of developing diabetic retinopathy and its progression among patients with T2DM. More importantly, we found that individualization of targets and communication between health professionals and patients may be important characteristics for successful interventions. We recommend to develop strategies to enable ophthalmologists and diabetes health professionals to work together with patients. These strategies may enable the health professionals to provide more personalized health advice and to help the patients set more individualized targets.

Healthy ageing

Instead of merely focusing on treating health conditions, the results of our study suggest that more focus on prevention as well as better self-management of health conditions can be beneficial to promoting healthy ageing. Healthy lifestyle, social support and social engagement may be important factors to prevent and control health conditions. Therefore, we recommend to develop strategies to promote healthy lifestyle, social support and social engagement.

9.5 GENERAL CONCLUSION

This thesis focusses on health promotion for people with frailty and chronic conditions:

First, the physical, psychological and social frailty each have a negative association with both physical and mental HRQoL. Maintaining a regular frequency of physical activity and (if not present) increasing to a regular frequency of physical activity are associated with maintaining or improving the level of physical, psychological and social frailty. The TFI, a self-report questionnaire that assesses physical, psychological and social domains of frailty, has been shown to be reliable and valid in Spain, Greece, Croatia, the Netherlands and the UK. Lack of confidence regarding unfamiliar care providers, may be a barrier to engage in certain preventive care activities; this may be a barrier towards adequate use of coordinated prevented care among older people.

Second, peer support may be effective with regard to glycemic control for patients with T2DM. Curriculum-combined-reinforcement-intervention and Home-visit-intervention are suggested according to the results of our study. Multifactorial interventions with individualized targets and communication between health professionals and patients are more effective than other interventions in the prevention and control of diabetic retinopathy.

Furthermore, we developed and implemented an intervention combining the concepts of mindfulness, social engagement and ICT support to reduce the burden of citizens with chronic conditions in 4 European countries.

We suggest future research on the development and effects of interventions to target people at an earlier age to prevent frailty in later life, and to promote healthy ageing. On-going support may be important for the prevention and better management of frailty and chronic conditions. We recommend to develop strategies to enable sustainability of newly developed (effective) approaches.

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Chapter 10

Summary and samenvatting

SUMMARY

Frailty is increasingly recognized as one of the most serious public health challenges today. Frailty is a multidimensional concept with physical, psychological and social factors playing a role in its development. The Tilburg Frailty Indicator (TFI) is a multidimensional frailty measure which includes 15 items addressing 3 domains: the physical, psychological and social domains. However, many studies related to frailty focused on physical frailty only, and more studies on the psychological and social frailty are needed to provide insight regarding the determinants of, and the management of frailty. On-going changes in lifestyle including diet, exercise, medication management and monitoring clinical preventive parameters have shown to be effective in better management and control of chronic conditions, such as type 2 diabetes (T2DM), as well as their complications. However, there are relatively few studies regarding the effectiveness of interventions among adults with chronic conditions to promote self-management. With this thesis, we aimed to answer the following research questions:

1. What is the association between physical, psychological and social frailty and health-related quality of life (HRQoL) among community-dwelling older adults? (Chapter 2)
2. What are the longitudinal associations between physical activity and frailty as well as the association between a 12-month change in physical activity and frailty among community-dwelling older adults? (Chapter 3)
3. What are the reliability and validity of the Tilburg Frailty Indicator (TFI) in five European countries? (Chapter 4)
4. How does the Urban Health Centres Europe (UHCE) approach perform in terms of specific process components? (Chapter 5)
5. What are the effects of peer support on glycemic control for adults with T2DM and the characteristics of effective peer support? (Chapter 6)
6. What are the effects of interventions targeting modifiable risk factors on diabetic retinopathy for adults with T2DM and the characteristics of effective interventions? (Chapter 7)
7. Could the Social Engagement Framework for Addressing the Chronic-disease-challenge (SEFAC) intervention be effective to promote the self-management of chronic conditions and a healthy lifestyle? (Chapter 8)

Chapter 2-5 use data of UHCE project which aimed to improve the management of multi-morbidity of community-dwelling older people in five European countries using integrated care pathways that focus on adherence to treatment and prevention of falls and frailty. Chapter 6-7 use data from PubMed, ScienceDirect, Web of scienceand/or Embase. Chapter 8 uses data of SEFAC project which aimed to empower citizens at risk of or with T2DM and/or cardiovascular disease (CVD) to self-manage their chronic conditions through the SEFAC intervention.

In **Chapter 2**, the association between physical, psychological and social frailty and HRQoL was studied. The results showed that physical, psychological and social frailty each has a

negative association with both physical and mental HRQoL. The associations between social frailty and both physical and mental HRQoL remained significant when controlling for physical and psychological frailty.

In **Chapter 3**, the longitudinal association between frequency of moderate physical activity and overall, physical, psychological and social frailty as well as the association between a 12-month change in frequency of moderate physical activity and frailty were studied. Our results showed that both maintaining a regular frequency of physical activity and increasing to a regular frequency of physical activity are associated with maintaining or improving the level of frailty, not only in the physical domain, but also in the psychological and social domains of frailty.

In **Chapter 4**, the reliability and validity of the full TFI and its three domains were assessed. Our study supported the reliability and validity of the full TFI and physical domain. The TFI may be applied as an instrument to measure frailty in community-dwelling older adults for large-scale population studies on frailty in the five European countries

In **Chapter 5**, process components of the implementation of the UHCE approach were evaluated using the Steckler and Linnan framework. The findings indicate that people in poor health might have enrolled less often and that care activities requiring transport or a higher level of activity might not reach older people who are limited in their functioning. Finally, mistrust towards unfamiliar care providers and lack of confidence to engage in certain care activities were observed to be main barriers towards engagement in care among older people.

In **Chapter 6**, the effects of peer support on glycemic control for patients with T2DM and the important characteristics among providers, types, intervention duration and effect duration were studied through a meta-analysis among relevant randomized control trials (RCTs). Peer support was found to achieve modest but statistically significant benefits on glycemic control for patients with T2DM. Peer support provided by patients themselves as a group or provided by nonprofessionals like community workers may have significantly better effect.

In **Chapter 7**, the effects of interventions targeting modifiable risk factors of diabetic retinopathy (blood glucose, blood pressure, lipid, dietary, physical activity and smoking) as well as the important characteristics of effective interventions were studied through a meta-analysis among relevant RCTs. A multifactorial intervention with an individualized approach and communication between health professionals and patients was more effective than other interventions in the prevention and control of diabetic retinopathy.

In **Chapter 8**, the evaluation design of the SEFAC project was described. The SEFAC project aimed to improve the self-management of citizens at risk of or with T2DM and/or CVD in four European countries using the SEFAC intervention. The intervention combines the concepts of mindfulness, social engagement and ICT support. The evaluation design includes the effects of the SEFAC intervention on self-management, healthy lifestyle behaviors, social support,

stress, depression, sleep and fatigue, adherence to medications and HRQoL. The evaluation design also includes the (cost-) effectiveness of the SEFAC intervention.

The findings of this thesis provide directions for future research and implications for policy and practice. We suggest future research on the development of interventions targeting people at an earlier age to prevent frailty. On-going support is important for better management of frailty and chronic conditions. We recommend to develop strategies to enable the sustainability of newly developed (effective) approaches. We suggest more focus on the prevention of disease as well as better self-management of conditions to create an environment to promote health and improve people's wellbeing.

SAMENVATTING

Kwetsbaarheid van ouderen (Engelse woord: frailty) wordt steeds meer gezien als één van de grootste uitdagingen op het gebied van de hedendaagse volksgezondheid. Kwetsbaarheid is een multidimensionaal begrip waarin fysieke, psychologische en sociale factoren een rol spelen. De Tilburg Frailty Indicator (TFI) is een instrument dat kwetsbaarheid multidimensionaal meet. De vragenlijst bestaat uit 15 items die betrekking hebben op 3 domeinen: het fysieke, psychologische en sociale domein. Veel onderzoek op het gebied van kwetsbaarheid van ouderen richt zich uitsluitend op de fysieke kwetsbaarheid. Om inzicht te krijgen in voorspellers van kwetsbaarheid en het beheer van kwetsbaarheid, is meer onderzoek nodig naar de psychische en sociale kwetsbaarheid van ouderen. Veranderingen in leefstijl, waaronder voeding, lichaamsbeweging en medicatiebeheer, zijn effectief gebleken bij het beheren en monitoren van chronische aandoeningen, zoals type 2 diabetes (T2DM). Er is echter relatief weinig onderzoek gedaan naar de effectiviteit van zelfmanagement om chronische aandoeningen te beheren en monitoren. Met dit proefschrift wilden wij de volgende onderzoeksvragen beantwoorden:

1. Wat is de associatie tussen fysieke, psychologische en sociale kwetsbaarheid en gezondheidsgerelateerde kwaliteit van leven bij zelfstandig wonende ouderen? (Hoofdstuk 2)
2. Wat zijn de longitudinale associaties tussen fysieke activiteit en kwetsbaarheid en tussen een verandering in fysieke activiteit en kwetsbaarheid bij zelfstandig wonende ouderen? (Hoofdstuk 3)
3. Wat zijn de betrouwbaarheid en validiteit van de Tilburg Frailty Indicator (TFI) in vijf Europese landen? (Hoofdstuk 4)
4. Hoe presteert de 'Urban Health Centers Europe' (UHCE) benadering wanneer gekeken wordt naar specifieke procescomponenten? (Hoofdstuk 5)
5. Wat zijn de effecten van peer support op glykemische controle voor volwassenen met T2DM en wat zijn de kenmerken van effectieve peer support? (Hoofdstuk 6)
6. Wat zijn de effecten van interventies gericht op veranderbare risicofactoren op diabetische retinopathie voor volwassenen met T2DM en wat zijn belangrijke kenmerken van effectieve interventies? (Hoofdstuk 7)
7. Kan de 'Social Engagement Framework for Addressing the Chronic-disease-challenge' (SEFAC) interventie effectief zijn in het bevorderen van zelfmanagement van chronische aandoeningen en een gezonde leefstijl? (Hoofdstuk 8)

In hoofdstuk 2-5 werden gegevens gebruikt van het UHCE-project dat het beheer van multimorbiditeit bij zelfstandig wonende ouderen beoogde te bevorderen. In hoofdstuk 6-7 werden gegevens van PubMed, ScienceDirect, Web of science en/of Embase gebruikt. In hoofdstuk 8 werden gegevens van het SEFAC-project gebruikt dat het zelfmanagement van burgers met (risico op) T2DM en/of hart- en vaatziekten beoogde aan te moedigen.

In **Hoofdstuk 2** is de associatie tussen fysieke, psychische en sociale kwetsbaarheid en gezondheidsgerelateerde kwaliteit van leven onderzocht. De resultaten toonden aan dat fysieke, psychologische en sociale kwetsbaarheid elk een negatieve associatie hebben met zowel fysieke als mentale kwaliteit van leven. De associaties tussen sociale kwetsbaarheid en fysieke en mentale kwaliteit van leven bleven significant na correctie voor fysieke en psychische kwetsbaarheid.

In **Hoofdstuk 3** is de longitudinale associatie tussen de frequentie van matige fysieke activiteit en kwetsbaarheid onderzocht, evenals de associatie tussen een verandering in de frequentie van fysieke activiteit en kwetsbaarheid over een periode van 12 maanden. Zowel het behouden van een regelmatige frequentie als het verhogen naar een regelmatige frequentie van fysieke activiteit was geassocieerd met het behouden of verbeteren van het fysieke, psychologische en sociale kwetsbaarheidsniveau.

In **Hoofdstuk 4** werden de betrouwbaarheid en validiteit van de volledige TFI en van de drie afzonderlijke domeinen beoordeeld. De volledige TFI en het fysieke domein bleek betrouwbaar en valide te zijn. De TFI kan worden gebruikt als een instrument om de kwetsbaarheid van zelfstandig wonende ouderen te meten in grootschalig bevolkingsonderzoek in de vijf Europese landen.

In **Hoofdstuk 5** werden specifieke procescomponenten van de UHCE-aanpak geëvalueerd met het raamwerk van Steckler- en Linnan. Mensen met een slechte gezondheid deden mogelijk minder vaak mee aan het UHCE-project. Activiteiten waarvoor vervoer of een hoger activiteitsniveau nodig was, waren mogelijk niet toegankelijk voor ouderen die beperkt waren in hun functioneren. Tenslotte werden wantrouwen richting onbekende zorgverleners en gebrek aan vertrouwen in bepaalde zorgactiviteiten waargenomen als belangrijkste belemmeringen om deel te nemen aan zorg.

In **Hoofdstuk 6** werden de effecten van peer support op glykemische controle voor volwassenen met T2DM en de belangrijke kenmerken van effectieve peer support bestudeerd. Peer support bleek bescheiden, maar statistisch significante, voordelen te hebben op de glykemische controle voor patiënten met T2DM. Peer support van een groep patiënten of van niet- zorgprofessionals, zoals maatschappelijk werkers, kan een aanzienlijk beter effect hebben.

In **Hoofdstuk 7** werden de effecten van interventies gericht op veranderbare risicofactoren van diabetische retinopathie (bloedglucose, bloeddruk, lipiden, voeding, lichaamsbeweging en roken) alsook de belangrijke kenmerken van effectieve interventies bestudeerd. Een multifactoriële interventie met een persoonlijke aanpak en communicatie tussen zorgprofessionals en patiënten was effectiever dan andere interventies voor de preventie en het beheer van diabetische retinopathie.

In **Hoofdstuk 8** werd het raamwerk van de evaluatie van het SEFAC-project beschreven. Het SEFAC-project beoogde het zelfmanagement van burgers met (risico op) T2DM en/of hart- en vaatziekten aan te moedigen in vier Europese landen. De interventie combineert mindfulness, maatschappelijke betrokkenheid en ICT-ondersteuning. Het raamwerk omvat de effecten van de SEFAC-interventie op zelfmanagement, gezonde leefstijl gedragingen, sociale steun, stress, depressie, slaap en vermoeidheid, medicatietrouw en kwaliteit van leven. Het raamwerk omvatte ook de (kosten-)effectiviteit van de SEFAC-interventie.

De bevindingen van dit proefschrift bieden aanwijzingen voor toekomstig onderzoek en implicaties voor beleid en praktijk. Om kwetsbaarheid op oudere leeftijd te voorkomen raden wij aan interventies te ontwikkelen die zich richten op mensen met een jongere leeftijd. Continue ondersteuning is belangrijk voor een beter beheer van kwetsbaarheid en chronische aandoeningen. We raden de ontwikkeling van strategieën aan die nieuw ontwikkelde (effectieve) benaderingen duurzaam maken. Meer aandacht voor ziektepreventie en beter zelfmanagement maken een omgeving mogelijk waarin gezondheid en welzijn van mensen wordt aangemoedigd.

A

Appendices

LIST OF ABBREVIATIONS

ABCD	Appropriate Blood Pressure Control in Diabetes
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation
ADL	Activities of daily living
AI	Artificial intelligence
AUC	Area under the ROC curve
AUDIT-C	Alcohol Use Disorder Identification Test
CCOI	Curriculum-only-intervention
CCRI	Curriculum-combined-reinforcement-intervention
CDSE-6	Short 6-item version of the Chronic Disease Self-Efficacy instrument
CG	Control group
CHWI	Community-health-worker-intervention
CI	Confidence interval
CVD	Cardiovascular Disease
DR	Diabetic retinopathy
ELISAN	European Local Inclusion and Social Action Network
EMC	Erasmus MC University Medical Center
EQ-5D-5L	EuroQol- 5 Dimensions- 5 level
ETDRS	the Early Treatment Diabetic Retinopathy Study
EU	European Union
GALI	the 1-item Global Activity Limitation Index
GARS	Groningen Activity Restriction Scale
GSE	General Self-Efficacy scale
GRADE	Grades of Recommendations Assessment, Development and Evaluation
HbA_{1c}	Glycated hemoglobin
HRQoL	Health Related Quality of Life
HVI	Home-visit-intervention
IADL	Instrumental activities of daily living
ICT	Information and Communication Technology
IG	Intervention group
IPAQ	International Physical Activity Questionnaire
ISCED	International Standard Classification of Education
MCS	Mental Component Summary
MHI-5	full 5-item mental well-being scale of the 36-Item Short Form Survey
NL	the Netherlands
NSES	Nutrition Self-Efficacy Scale
OR	Odds Ratios
OSS-3	Oslo Social Support scale
PA	Physical activity
PCQ	Productivity Costs Questionnaire
PCS	Physical Component Summary
PESES	Physical Exercise Self-Efficacy Scale

PHQ-8	8-item Patient Health Questionnaire depression scale
PPI	Peer-partner-intervention
PSS-10	10-item Perceived Stress Scale
RCTs	Randomized controlled trials
ROC	Receiver operating characteristic
SEFAC	Social Engagement Framework for Addressing the Chronic-disease-challenge
SF-12	12-item Short Form health survey
SGI	Support-group-intervention
SHARE-FI	Survey of Health, Ageing and Retirement in Europe-Frailty Instrument
short-JG	De Jong Gierveld loneliness scale
SMAQ	Short Medication Adherence Questionnaire
SMRC	Self-Management Resource Center
T2DM	Type 2 Diabetes Mellitus
TDI	Telephone-dominant-intervention
TFI	Tilburg Frailty Indicator
UHCE	Urban Health Centres Europe
UK	the United Kingdom
UKPDS	UK Prospective Diabetes Study
VADT	Veterans Affairs Diabetes Trial
WHO	World Health Organization

LIST OF PUBLICATIONS

X. Zhang, S. S. Tan, C. B. Franse, L. Bilajac, T. Alhambra-Borras, J. Garces-Ferrer, A. Verma, G. Williams, G. Clough, E. Koppelaar, T. Rentoumis, R. van Staveren, A. J. J. Voorham, F. Mattace-Raso, A. van Grieken and H. Raat (2020). "Longitudinal Association Between Physical Activity and Frailty Among Community-Dwelling Older Adults." J Am Geriatr Soc; In press (*This thesis*)

X. Zhang, S. S. Tan, L. Bilajac, T. Alhambra-Borrás, J. Garcés-Ferrer, A. Verma, E. Koppelaar, A. Markaki, F. Mattace-Raso, C. B. Franse, H. Raat (2020). "Reliability and Validity of the Tilburg Frailty Indicator in 5 European Countries. " Journal of the American Medical Directors Association ; 21(6):772-779.e6. (*This thesis*)

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ABOUT THE AUTHOR

Xuxi Zhang was born on February 17th 1991, in Zibo, Shandong Province, China. After graduating from Shandong Zibo Shiyan High School in 2009, she started her bachelor studies with a major in Biomedical English, in Health Science Center of Peking University, Beijing, China. During her bachelor studies, Xuxi studied a second major in Intellectual Property, in Law School of Peking University. In June 2014, she graduated with a Bachelor in Science as well as a Bachelor in Law. In the same year, she continued to study at Peking University as a Master student in School of Public Health. In June 2017, she obtained her master degree in Public Health. In September 2017, she started her PhD project at Erasmus University Medical Center in Rotterdam, the Netherlands. Xuxi received a fellowship from the China Scholarship Council (CSC) to perform her PhD project in the Netherlands. From 2017 to 2020, she worked under the supervision of Prof. Hein Raat and Dr. Siok Swan Tan in the Department of Public Health. Her research mainly focused on healthy ageing and health promotion in people with frailty and chronic conditions, the results of which are presented in the present thesis. In the future, Xuxi determines to develop her career in academia and devote herself to the research to improve population health, especially for older people and people with chronic conditions.

PHD PORTFOLIO

Name PhD student	Xuxi Zhang
Departments	Public Health, Erasmus Medical Center Rotterdam
Research school	Netherlands Institute for Health Sciences (NIHES), Rotterdam
PhD period	September 2017-September 2020
Promotor	Prof. dr. Hein Raat
Co-promotor	Dr. Siok Swan Tan

	Year	Workload (ECTS/Hours)
1. PhD training		
General Courses		
Biostatistical Methods I: Basic Principles	2017	5.7 ECTS
Reviews: Project management, multiple databases and EndNote, Medical Library, Erasmus MC	2019	0.1 ECTS
Systematic Literature Retrieval in embase, Medical Library, Erasmus MC	2019	0.1 ECTS
Systematic Literature Retrieval (in PubMed)-Part 1, Medical Library, Erasmus MC	2019	0.1 ECTS
Systematic Literature Retrieval (in PubMed)-Part 2, Medical Library, Erasmus MC	2019	0.1 ECTS
Scientific Integrity, Erasmus MC	2019	0.3 ECTS
Specific Courses		
Dutch A1	2017	1.0 ECTS
Logistic Regression	2018	1.4 ECTS
Advanced Medical Writing and Editing	2018	0.7 ECTS
Causal inference	2019	1.4 ECTS
Primary and secondary prevention research	2019	0.7 ECTS
Markers and prediction research	2019	0.7 ECTS
Teaching in English	2019	1.0 ECTS
Basic Course on 'R'	2019	2.0 ECTS
Biomedical English Writing	2020	2.0 ECTS
Presentations		
Oral Presentation, The 19th International Conference on Integrated Care, San Sebastián, Spain	2019	12 hours
Oral Presentation, the International Society of Behavioral Nutrition and Physical Activity (ISBNPA) 2019 Annual Meeting, Prague, the Czech Republic; The	2019	12 hours

abstract was awarded the conference's best student abstract on ageing		
Poster Presentation, ISBNPA 2019 Annual Meeting, Prague, the Czech Republic	2019	8 hours
Seminars and workshops		
Seminar, Department of Public Health	2017-2020	4.0 ECTS
Research Meeting Youth Section	2017-2020	2.0 ECTS
Youth Section Meeting	2017-2020	2.0 ECTS
Intrinsic Capacity Joint Webinar WHO & EU FrailSafe	2019	0.04 ECTS
Inter(national) conferences		
20th EUSUHM Youth Health Care in Europe, Rotterdam, the Netherlands	2019	0.5 ECTS
ISBNPA 2019 Annual Meeting, Prague, the Czech Republic	2019	1.3 ECTS
Health(y) Sciences First Health Sciences Research Day, Rotterdam, the Netherlands	2019	0.3 ECTS
The 19th International Conference on Integrated Care, San Sebastián, Spain	2019	1.0 ECTS
ISBNPA 2018 Annual Meeting, Hongkong, China	2018	1.3 ECTS
Improving Implementation Practice: a one-day implementation science conference, Amsterdam, the Netherlands	2018	0.3 ECTS
the Catalysts for Change symposium, Utrecht, the Netherlands	2018	0.3 ECTS
2. Other activities		
Advise, aid with methodology and co-author colleagues	2017-2019	40 hours
Peer-review for journals: BMJ Open and Diabetes Research and Clinical Practice	2017-2019	8 hours

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