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The uptake and effectiveness of a tailor-made online lifestyle program targeting modifiable risk factors for dementia among middle-aged descendants of people with recently diagnosed dementia: study protocol of a cluster randomised controlled trial (Demin study)

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The uptake and effectiveness of a tailor-made online lifestyle program targeting modifiable risk factors for dementia among middle-aged descendants of people with recently diagnosed dementia: study protocol of a cluster randomised controlled trial (Demin study)

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ABSTRACT

Introduction Descendants of dementia patients have a higher risk to develop dementia. This study aims to investigate the uptake and effectiveness of an online tailor-made lifestyle program for Dementia Risk Reduction (DRR) among middle-aged descendants of people with recently diagnosed late-onset dementia.

Methods and analysis Demin is a cluster randomised controlled trial, aiming to include 21 memory clinics of which thirteen will be randomly allocated to the passive (poster and flyer in waiting room) and eight to the active recruitment strategy (additional personal invitation by members of the team of the memory clinic). We aim to recruit 378 participants, aged 40-60 years, with a parent who is recently diagnosed with Alzheimer's Disease or Vascular Dementia at one of the participating memory clinics. All participants receive a dementia risk assessment (online questionnaire, physical examination and fasting blood sample) and subsequently an online tailor-made lifestyle advice regarding protective (Mediterranean diet, low/moderate alcohol consumption, high cognitive activity) and risk factors (physical inactivity, smoking, loneliness, cardiovascular disease, hypertension, high cholesterol, diabetes, obesity, renal dysfunction, depression) for dementia. The primary outcome is the difference in uptake between the two recruitment strategies. Secondary outcome measures are the change(s) in 1) the Lifestyle for Brain Health (LIBRA) score, 2) individual health behaviours, 3) health beliefs and attitudes towards DRR and 4) compliance to the tailor-made lifestyle advice and that of the general practitioner. Outcomes will be measures at 3, 6, 9 and 12 months after baseline assessment. The effectiveness of this online tailor-made lifestyle program will be evaluated by comparing Demin participants to a matched control group (Lifelines cohort).

Ethics and dissemination This study has been approved by the Dutch Ministry of Health, Welfare and Sport according to the Population Screening Act. All participants have to give online informed consent using SMS-tan.

Trial registration number NTR7434

ARTICLE SUMMARY

Strengths and limitations of this study

- This is the first multicentre trial that focuses on dementia risk reduction in middle-aged descendants of recently diagnosed patients with Alzheimer's disease or Vascular dementia.
- The program gives participants insight in their risk and protective factors for dementia and provides a tailor-made online lifestyle advice with regard to thirteen modifiable risk factors for dementia, taking the stages of (health behaviour) change into account.
- The application ensures the privacy of the participants by using SMS-tan for logging in their personal account and signing the electronic informed consent form.
- The web-based application (demin.nl) functions fully automatically, making it easy to implement the study in other memory clinics and settings.
- Changing health behaviour is difficult and it is unclear whether a tailor-made online lifestyle advice is sufficient to change health behaviour and to maintain a healthy lifestyle.

KEY WORDS

Dementia

Health behavior

Risk reduction behavior

Lifestyle

Middle aged

INTRODUCTION

Dementia is considered a major public health concern [1]. Due to the ageing population the number of dementia cases will increase substantially in the next decades. In 2015, more than 46 million people worldwide were affected by dementia and this number is expected to increase to 131 million by 2050 [2]. This rise in people with dementia carries a high economic and social burden for society [1]. In 2015, global costs of dementia reached 818 billion US dollars and will increase further [3]. Currently, no curative treatments are available. Therefore, prevention is a key element to counteract the dementia epidemic [4,5].

The most common types of dementia are Alzheimer's disease (AD) (60-70%) ,Vascular dementia (VD) (15-20%) or a combination of AD and VD (mixed dementia) [6–8]. The presence of a first-degree relative with AD doubles the risk for developing AD [9]. This increased risk has several reasons. Firstly, descendants of people with AD more often have a higher genetic predisposition for AD (e.g. carrier of the Apo lipoprotein E (APOE) ε4 allele) [9]. Secondly, high blood pressure, vascular diseases and other vascular risk factors (i.e. diabetes type 2, obesity, hypercholesterolemia) often cluster in families [10]. Lastly, psychosocial behaviour runs in the family and also affects health behaviour and lifestyle [11,12]. Not surprisingly, individuals with a parent who is recently diagnosed with AD or VD often worry about their own risk of developing dementia. Therefore, this life event (parental diagnosis of dementia) might encourage the willingness of individuals to change their health behaviour [13].

Parental family history has been associated with an increased risk of dementia independently of known genetic risk factors [9,14]. Therefore, a healthy lifestyle might be beneficial for individuals with a positive family history. Over the last decade, evidence of modifiable risk factors for dementia has been mounting [4,6,15]. The Lancet commission on dementia prevention, intervention and care demonstrated that 35% of the dementia cases is attributable to modifiable risk factors (i.e. less education, hearing loss, midlife hypertension, midlife obesity, smoking, depression, physical inactivity, social isolation and diabetes) and recommended to start interventions including more

childhood education, promotion of physical exercise, reduction of smoking, maintaining social engagement and management of hypertension, diabetes, obesity, depression and hearing loss [4,6,16]. Other major risk factors are hyperlipidaemia, coronary heart disease, renal dysfunction, Mediterranean diet and cognitive activity [15].

Only few studies examined the effectiveness of targeting these modifiable factors on cognitive decline and dementia incidence through a multi-domain intervention, such as the (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability) FINGER study [17], the (Prevention of Dementia by Intensive Vascular care) PreDIVA study [18] and the (The Multi-domain Alzheimer Preventive Trial) MAPT study [19]. These studies, with a follow-up varying from two to six years, found small or non-significant effects on cognition in older participants (e.g. >60 years) [17–19]. Starting multi-domain interventions earlier in life might be promising as cognitive decline begins already in midlife [20,21]. Furthermore, tailoring interventions improves the effectiveness of health behaviour change interventions [22]. Web-based interventions have the potential to support health behaviour change as there is the opportunity to tailor lifestyle advice [23–26]. They were especially effective when a theoretical basis or conceptual framework (e.g. Health belief model (HBM), Trans theoretical model (TTM), Theory of planned behaviour (TPB), I(integrated)-Change model [27–31]), behaviour change techniques (e.g. providing feedback on performance and information on the consequences of unhealthy behaviour) and several modes of delivery had been used [32]. Additionally, the effectiveness of web-based interventions is enhanced by using automated follow-up messages by email of text message (SMS) [22].

A challenge of health behaviour change interventions is to achieve a high level of uptake for screening (e.g. assessing risk and protective factors for dementia). A systematic review identified a large variation in uptake in health checks and lifestyle intervention programs [33], depending on the type of recruitment strategy. Uptake also depends on other factors as described in social cognition models (e.g. knowledge, perceived susceptibility and severity, facilitators, barriers and attitude towards such interventions) [27–31]. Therefore, information on dementia, the risk and protective factors for

dementia, heritability, and how to tackle risk and protective factors for dementia are important factors in the development of a web-based intervention.

To our knowledge, none of the health behaviour intervention studies were aimed at a specific group of middle-aged adults with increased risk for dementia due to their positive parental family history for dementia. Therefore, this study aims to investigate the uptake and effectiveness of a tailor-made online lifestyle program for dementia risk reduction among middle-aged descendants of recently diagnosed (in the last six months) people with AD or VD in the Netherlands. It is expected that middle-aged descendants of recently diagnosed people with AD or VD are more willing to assess their risk and motivated to adopt a healthier lifestyle as they just realized their (family) risk.

METHODS AND ANALYSIS

Study setting and design

This study is a pragmatic cluster randomized controlled trial (RCT), including 21 participating memory clinics in the Netherlands who are randomly allocated to a passive or active recruitment of participants. Memory clinics allocated to the active recruitment strategy invite potential participants face-to-face by a member of the team of the memory clinic to participate in the tailor-made online lifestyle program for dementia risk reduction (also called the Demin study), next to posters and flyers that are placed in the waiting room of the memory clinic. Memory clinics allocated to the passive recruitment strategy, do not invite potential participants pro-actively, but invite potential participants to participate in the Demin study by posters and flyers that are placed in the waiting room of the memory clinic.

Patients with AD or VD (or their caregivers) receive an envelope either at the registration desk of the memory clinic or after the consult of the patient (only with active recruitment). This envelope is addressed to the middle-aged descendants of patients with recently diagnosed AD or VD and includes a patient information form (PIF) with information about the content of the study, the advantages and disadvantages of study participation and how potential participants can participate. Potential

participants (one family member per patient) are asked to register themselves (e.g. making an account) on the Demin website (www.demin.nl), by using the memory clinic specific login access code, which is reported on the front page of the PIF and represents the memory clinic in which the parent was diagnosed. The decision to participate is confirmed by the participants by signing the online informed consent form (electronic signature by using SMS-tan). After signing this form, individuals from both recruitment strategies are able to log in to their personalized website 'My Demin' and continue the intervention in an equal manner. The personalized website 'My Demin' is secured and only accessible for the participant by logging in with their personal e-mail address, password and SMS-tan code. 'My Demin' contains the following information: 1) My personal (account) information, 2) Message inbox, 3) My online questionnaires, 4) My personal health profile including online tailor-made lifestyle advice. After participants have completed the online questionnaire, they automatically receive a message with a request to make an appointment for physical examination including a fasting blood sample. Moreover, participants can invite siblings to participate in the study in 'My Demin'.
The functionalities provided by the Demin website are based on the literature and input we received from people with a parent with dementia (focus group discussions).

Randomization of memory clinics

To prevent contamination between the two recruitment strategies, randomization is performed at the level of the memory clinics. To enhance comparability between the intervention (participants of the active recruitment strategy) and control group (participants of the passive recruitment strategy), the memory clinics will be matched and randomised by a statistician, who is blind to the identity of the memory clinics and not involved in the study. Firstly, all participating memory clinics will be matched into pairs based on the following criteria: (i) number of newly diagnosed dementia (VD, AD or mixed dementia) patients seen per year (range vary from 60 to 350 patients per year) and (ii) the average social economic position (SEP) of the population living around the memory clinic (neighbourhood SEP), based on data from Statistics Netherlands [34]. Secondly, the matched memory clinics will be randomized (pairwise randomization) to an active recruitment strategy or passive recruitment strategy using a computer-generated random number list. As we expect a higher response rate in the active

recruitment strategy group, we use an active : passive recruitment strategy ratio of 8:13 (see sample size calculations).

Study population

Eligible participants are middle-aged individuals (40-60 years old) with a parent who is recently (less than 6 months ago) diagnosed with AD or VD (or mixed dementia) at one of the participating memory clinics in the Netherlands (see acknowledgement). Individuals should provide informed consent, be able to fill out an online Dutch questionnaire. Pregnant women are excluded from participation.

Sample size calculations

The primary outcome measure is uptake, which is defined as the percentage of eligible individuals that signed the online informed consent form and completed baseline assessment (online questionnaire and physical examination and a fasting blood sample). In order to detect a difference of 20% in uptake between the passive and active recruitment strategy (30% versus 50%), we need 94 participants in each group to achieve a power of 80% with alpha levels of 0.05 (total = 188 participants). To take cluster randomization into account, we use the formula 1+ ((n-1)*ICC) (inflation factor), where n is the average number of included participants per memory clinic and the ICC the Intra Class Correlation [35]. The ICC is unknown, but an ICC of 0.05 is a common value for cluster randomized controlled trials in hospitals [36]. The estimated average of included participants per memory clinic per year is n=15 using a passive recruitment strategy and n=25 using an active recruitment strategy, taking into account non-response. With unequal cluster sizes, 'n' is replaced by 'm', where m is the sum of $(M)^2/sum(M)$ $((15^2+25^2) / (15+25))$ [37]. This results in a sample size inflation factor of (1+ ((21.25-1)*0.05)= 2.01. Therefore, the total number of participants needed is 378 (2.01 * 188). In order to recruit 378 participants, we need 21 memory clinics, of which eight memory clinics (responsible for 189 included participants) will be allocated to the active recruitment strategy and thirteen memory clinics (responsible for 189 included participants) will be allocated to the passive recruitment strategy.

Demin website

The Demin website is available for everyone and provides information about dementia, heredity of dementia, risk and protective factors for dementia, and how to tackle potential risk factors for dementia. The health information will be provided by written text and in an audio-visual format, such as a spoken animation, to assure inclusion of participants with different levels of health literacy. [38].. According to the cognitive theory of multimedia learning (CTML), people process visual and auditory information through different channels [39,40]. It is known that health information provided by various channels, such as written text and spoken animations, improves information processing compared to information only provided through written text or spoken animations [39,40]. The instructions for registration (making an account, signing informed consent) are also provided as written text as visual screenshots representing the steps of the registration process.

Online tailor-made lifestyle program for dementia risk reduction

After participants give online informed consent, participants have access to the online tailor-made lifestyle program for dementia risk reduction, which consists of 1) a dementia risk assessment and 2) an online tailor-made lifestyle advice including a personal health profile targeting risk and protective factors for dementia.

1. Dementia risk assessment

The dementia risk assessment consists of filling out an online questionnaire (in 'My Demin') and physical examination, including a fasting blood sample, at one of the 21 participating memory clinics in order to determine whether risk and protective factors are present. In order to minimize the amount of missing data, validation and skip-and-fail rules were implemented in the online questionnaire. Furthermore, automatic reminders are sent to the participant if the online questionnaire was not filled in within two weeks. Physical examination will be conducted by the team of the local memory clinic and includes the following measurements: height (in cm) (SECA 222 stadiometer), body weight (in kg) without shoes (SECA 761 scale), waist- and hip circumference (in cm) (SECA 200 measuring tape), and three measurements of diastolic and systolic blood pressure (in mmHg) (Welch Allyn 'Spot Vital Signs' [41]). After physical examination, which takes approximately 15 minutes, a fasting blood

sample (maximum of 21 ml) is taken for direct laboratory measurement of glucose, HbA1C, total cholesterol, High-density-lipoprotein (HDL), Low-density-lipoprotein (LDL), triglycerides and serum creatinine. The results of the physical examination (height, body weight, blood pressure, waist- and hip circumference) are sent to the researcher (J. Vrijsen) to check the entry of the results by the participants. The results of the direct laboratory measurements are sent to the medical doctor (E.M. Abma) of the University Medical Centre Groningen to check for deviating values.

Risk and protective factors for dementia

Through the online questionnaire and physical examination, data on thirteen currently known protective (i.e. Mediterranean diet, low/moderate alcohol consumption, cognitive activity) and risk factors (i.e. physical inactivity, smoking, loneliness, cardiovascular diseases, hypertension, high cholesterol, diabetes mellitus, obesity, renal dysfunction, depression) for dementia are collected [6,15,42]. See **Table 1** for an overview of the assessment measures. The measurements of these risk and protective factors are described in **Supplementary file 1**.

Table 1. Assessment measures at baseline and follow up

	Baseline	**3 months**	**6 months**	**9 months**	**12months**
RISK AND PROTECTIVE FACTORS					
Smoking	Q	Q	Q	Q	Q
Physical inactivity (SQUASH, IPAQ)	Q	Q	Q	Q	Q
Mediterranean diet (FFQ)	Q	Q	Q	Q	Q
Alcohol consumption (FFQ)	Q	Q	Q	Q	Q
High cognitive activity (CRIq)	Q	Q	Q	Q	Q
Loneliness (de Jong Gierveld, 6-item)	Q	Q	Q	Q	Q
Cardiovascular diseases (CVD)	Q	Q	Q	Q	Q
Obesity (body weight, height)	Q+ PE	Q	Q	Q	Q+PE
Hypertension (SBD, DBP)	Q+PE	Q	Q	Q	Q+PE

High cholesterol (LDL, HDL, TC)	Q+FBS	Q	Q	Q	Q+FBS
Diabetes Mellitus (glucose, HbA1C)	Q+FBS	Q	Q	Q	Q+FBS
Renal dysfunction (eGFR)	Q+FBS	Q	Q	Q	Q+FBS
Depression (CES-D)	Q	Q	Q	Q	Q

SQUASH Short Questionnaire to Assess Health-enhancing physical activity, *IPAQ* International Physical Activity Questionnaire, *FFQ* Food Frequency Questionnaire, *CRIq* Cognitive Reserve Index questionnaire (adapted), *CVD* Cardiovascular diseases, *SBP* Systolic Blood Pressure, *DBP* Diastolic Blood Pressure, *HDL* high-density lipoproteins, *LDL* low-density lipoproteins, *TC* total cholesterol, *HbA1C* Haemoglobin A1C, *eGFR* estimated Glomerular Filtration Rate, *CES-D* Centre for Epidemiological Studies Depression Scale

Q: Online questionnaire, PE: Physical examination, FBS: Fasting blood sample

2a. Personal health profile

After completion of the baseline dementia risk assessment (including the data entry of the physical examination and laboratory measurements), a personal health profile is automatically provided in the personal account of the participants (My Demin). The personal health profile gives an overview of the presence of the risk and protective factors for dementia. According to the Lifestyle for Brain Health (LIBRA) score, each risk and protective factor [15,42,43] is categorized into one of the following categories: 1) room for improvement, 2) remember to manage well, 3) keep this up (see **Table 2**). The "Keep this up" category represent factors that participants are currently managing well or diseases they do not have. The "Room for improvement" category represents the factors that could be improved by health behaviour change (e.g. quit smoking, become more physical active, change diet, drink less alcohol). The category "Remember to manage well" is assigned when a risk factor (i.e. cardiovascular disease, hypertension, high cholesterol, diabetes mellitus, renal dysfunction and depression) is present, but the disease is managed well as participants have regular meetings with their general practitioner for disease control (diabetes mellitus) or use medication for disease management (cardiovascular disease, hypertension, high cholesterol, renal dysfunction and depression) (see **Figure 1**).

[INSERT FIGURE 1 ABOUT HERE]

284 **Table 2.** Definition for the 3 categories in the personal health profile at baseline

Modifiable risk factors	Keep this up	Remember to manage well	Room for improvement
Diet	MIND-diet score = 14 points	n.a.	MIND-diet score < 14 points
Alcohol consumption	Average number of units of alcohol per week ≤ 7 and number of units per day is: ≤ 3 for women or ≤ 4 for men	n.a.	Average number of units of alcohol per week > 7 or number of units per day is: > 3 for women or > 4 for men
Cognitive activity	paid working hours ≥ 24 or CRIq score ≥ 50	n.a.	paid working hours < 24 and CRIq score < 50
Physical activity	(MVPA / week ≥ 150 and Sitting time ≤ 8 hours / day) or (MVPA / week < 150 and sitting time < 4 hours / day)	n.a.	(Sitting time > 8 hours / day) or (Sitting time ≥ 4 hours / day and MVPA / week < 150)
Smoking	Past or never smoker	n.a.	Current smoker
Loneliness	De Jong Gierveld score < 2	n.a.	De Jong Gierveld score ≥ 2
Cardiovascular diseases (CVD)	no CVD	at least one CVD and receives medical treatment	at least one CVD and no medical treatment
Weight	BMI ≥ 18.5 and BMI < 25.0	n.a.	BMI < 18.5 or BMI ≥ 25.0
Blood pressure	DBP < 90 mmHg and SBP < 140 and	DBP < 90 mmHg and SBP < 140 and	DBP ≥ 90 mmHg or

	no medical treatment	medical treatment	SBP ≥ 140 mmHg
Cholesterol	(LDL ≤ 2.5 mmol/l and TC/HDL ≤ 8) and no medical treatment	(LDL ≤ 2.5 mmol/l and TC/HDL ≤ 8) and medical treatment	LDL > 2.5 mmol/l or TC/HDL > 8
Diabetes Mellitus	glucose < 7.0 mmol and HbA1C ≤ 53 mmol/mol	(HbA1C ≤ 53 mmol/mol and medical treatment) or (glucose < 7.0 mmol and HbA1C > 53 mmol/mol and medical treatment)	(HbA1C > 53 mmol/mol and no medical treatment) or (glucose ≥ 7.0 mmol and HbA1C > 53 mmol/mol) or (glucose ≥ 7.0 mmol and HbA1C ≤ 53 mmol/mol and no medical treatment)
Kidney	eGFR ≥ 60 ml/min/1.73 m^2	eGFR < 60 ml/min/1.73 m^2 and medical treatment	eGFR < 60 ml/min/1.73 m^2 and no medical treatment
Depression	CES-D < 16 points	CES-D ≥ 16 points and medical treatment	CES-D ≥ 16 points and no medical treatment

MIND-diet Mediterranean-DASH Diet Intervention for Neurodegenerative Delay, *CRIq* Cognitive Reserve Index questionnaire, *MVPA* Moderate to vigorous physical activity, CVD Cardiovascular diseases, *BMI* Body mass index, *DBP* diastolic blood pressure, *SBP* systolic blood pressure, *LDL* low-density lipoproteins, *TC* total cholesterol, *HDL* high-density lipoproteins, *HbA1C* Haemoglobin A1C, *eGFR* estimated Glomerular Filtration Rate, *CES-D* Centre for Epidemiological Studies Depression Scale

2b. Tailor-made online lifestyle advice for dementia risk reduction

Participants also receive an online tailor-made lifestyle advice targeting risk factors associated with dementia and following the Dutch guidelines for a healthy diet, alcohol consumption, physical activity, diabetes mellitus, renal dysfunction and cardiovascular health including cholesterol levels and BMI [44–48]. For each risk and protective factor, information is given about (i) the norm (cut-off point for not having this risk factor), (ii) the association between the risk factor and dementia and (iii) lifestyle advice how to tackle this factor. The online lifestyle advice was tailored to the participants based on (i) the presence of risk factors, (ii) the strength of the association between the risk factors and dementia [15,42] and (iii) the stages of change of the health behaviour related risk factors (physical inactivity, diet, alcohol consumption, smoking behaviour, cognitive activity, social activity). The stages of change are determined by asking "Which statement fits best for you?", where each answer option reflects one of the following stages of change: pre-contemplation, contemplation, preparation, action and maintenance [28]. It is known that participants who are in the preparation and action stage are more willing to change their health behaviour, therefore lifestyle advice for these factors are given first [28].

In case medically relevant findings are found, including untreated diabetes mellitus (glucose ≥ 7.0 mmol/l or (glucose ≥ 6.1 mmol/l and HbA1C > 53 mmol/mol)), untreated renal dysfunction (estimated Glomerular Filtration Rate (eGFR) ≤ 60 ml/min/1.73 m2) and increased risk for developing cardiovascular diseases (CVD) (CVD risk ≥ 10% according to the Dutch SCORE formula [48]), participants receive, in addition to the online tailor-made lifestyle advice, a separate message in their personal inbox with the recommendation to contact their general practitioner to verify the results and discuss whether treatment is needed.

Outcome measures and measurements

Participants are invited to fill in the online questionnaire at baseline and four times (3, 6, 9 and 12 months after baseline measurement) during one year follow-up . Physical examination, including the fasting blood sample for direct laboratory measurements, is only done at baseline and 12 months after

baseline measurement (see **Supplementary file 2**). Data from the online questionnaires and physical examination are stored automatically in an electronic Case Report Form (eCRF) data management program, which is only accessible by the researchers involved in this study. Data from the direct laboratory measurement are entered manually in the electronic Case Report Form (eCRF) data management program. Every month, memory clinics are requested to provide information about 1) the number of eligible participants (e.g. new cases of AD and VD), 2) the number of envelopes that are given away, and 3) any difficulties with the recruitment of participants. In order to keep participating memory clinics involved in the study, every three months newsletters are sent around and memory clinics are contacted monthly to evaluate the uptake.

Primary outcome

The primary outcome is the difference in uptake (e.g. the percentage of eligible people that signed the online informed consent form and completed risk assessment of the total number of eligible people) between the active and passive recruitment strategy. The total number of eligible people in each recruitment group (active versus passive) are based on the number of new cases of AD or VD in all memory clinics during the recruitment period, assuming an average of one child per dementia patient receiving the envelope with the PIF including a login access number.

Secondary outcomes

Secondary outcomes include:

1) The change in Lifestyle for Brain Health (LIBRA) score. The LIBRA score has been validated among individuals in midlife and reflects an individual's potential to reduce their risk on developing late-onset dementia [42]. The LIBRA score consists of twelve currently known protective (i.e. Mediterranean diet, low/moderate alcohol consumption, cognitive activity) and risk factors (i.e. physical inactivity, smoking, cardiovascular diseases, hypertension, high cholesterol, diabetes mellitus, obesity, renal dysfunction, depression) for dementia (13, 14,31) and ranges from -5.9 (low risk for developing dementia) to 12.7 (high risk for developing dementia).

A one point increase in the LIBRA score is associated with a 19% higher risk for dementia [42,49]. The definitions and corresponding scores for the three protective and ten risk factors for dementia are described in **Table 3**.

Table 3. Definition of risk and protective factors for dementia in the LIBRA score and corresponding scores

Modifiable risk factors		**Definition**	**Score**
Protective factors			
1	High cognitive activity	Score ≥ 50 points on the Cognitive Reserve Index questionnaire (leisure time activities) (CRIq) or hours of paid work ≥ 24 hours	-3.2
2	Mediterranean diet	MIND-diet score (0-14) = 14 points	-1.7
3	Low/moderate alcohol consumption	Average number of glasses of alcohol a week ≤ 7 and number of glasses a day is: ≤ 3 glasses for women (no binge drinking) ≤ 4 glasses for men (no binge drinking)	-1.0
Risk factors			
4	Cardiovascular diseases (CVD)	Presence of at least one of the follow diseases: history of angina pectoris, myocardial infarction, transient ischemic attacks, stroke or peripheral arterial diseases	+1.0
5	Physical inactivity	Not fulfilling Dutch Norm for Physical activity defined as ≥ 150 min/week physical activity of moderate to vigorous intensity, measured with the SQUASH questionnaire	+1.1
6	Renal dysfunction	Estimated glomerular filtration rate ≤ 60 ml/min/1.73	+1.1
7	Diabetes Mellitus	Glucose (capillary blood) > 7.0 mmol/l or HbA1c > 53 mmol/mol	+1.3
8	High cholesterol	LDL > 2.5 mmol/l or TC/HDL ≥ 8	+1.4
9	Smoking	Current smoker	+1.5

10	Obesity	BMI ≥ 30	+1.6
11	Hypertension	SBP > 140 mmHg or DBP > 90 mmHg	+1.6
12	Depression	Score ≥ 16 points on the Centre for Epidemiologic Studies Depression scale (CES-D)	+2.1

LDL low-density lipoproteins*, TC* total cholesterol, *HDL* high-density lipoproteins*, BMI* Body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

2) The change in the individual health behaviours, including physical activity (minutes of MVPA per week), diet (MIND-diet score; 0-14), alcohol consumption (number of glasses of alcohol per week), smoking behaviour (current smoker (yes/no) and number of cigarettes/cigars a day), cognitive activity (leisure-time cognitive activity score and number of hours paid work), loneliness (overall loneliness score; 0-6) and social activity (number of contacts per two weeks) and their stage of change over time. The stages of change are categorized into pre-contemplation (1), contemplation (2), preparation (3), action (4) and maintenance (5) [28].

3) Changes in beliefs and attitudes with regard to dementia risk reduction are measured using the Motivation to Change Lifestyle and Health Behaviour for Dementia Risk Reduction Scale (MCLHB-DRR scale) [50,51]. The MCLHB-DRR scale is based on the Health Belief Model [27], which explains health-related behaviours. Seven subscales of the Health Belief Model were included: perceived susceptibility, perceived severity, perceived benefits, perceives barriers, cues to action, general health motivation and self-efficacy. Participants are asked to rate all items on a 5-point Likert scale, ranging from strongly disagree (score=1) to strongly agree (score=5). A minimum score of 23 and a maximum score of 115 can be achieved. A higher score reflects a higher motivation to change their lifestyle and health behaviour for dementia risk reduction. The Dutch version of the MCLHB-DRR scale, consisting of 23 items, has shown to be valid in the Dutch general population aged between 30 and 80 years old (unpublished observations, see **Supplementary file 3**).

4) Percentage of participants that indicated in the questionnaire that they have followed up the tailor-made online lifestyle advice ("On what risk factors did you receive lifestyle advice?" and "Did you follow up the tailor-made lifestyle advice since the last questionnaire (with regard to [risk factor])"? , but also the percentage of participants that indicated that they have followed up the advice to consult their General Practitioner ("Did you have contact with your general practitioner after receiving feedback on the risk and protective factors?").

Statistical analyses

First, descriptive characteristics will be explored. The difference in uptake between the two recruitment strategies will be examined using multilevel logistic regression analyses in order to correct for clustering at memory clinic level. We will calculate the percentage with the corresponding 95% confidence interval (CI) and use an alpha of 0.05 to test statistical significance.

The effectiveness of the online tailor-made lifestyle program for dementia risk reduction will be determined by, firstly comparing the change in LIBRA score, the individual risk factors and the MCLHB-DRR score between the active and passive recruitment strategy, and secondly comparing participants of the Demin study (active and passive recruitment strategy) to a control group consisting of Lifelines participants (large population-based cohort study (n> 167.000)) (www.lifelines.nl)[52] in outcome. Lifelines participants (age 40 – 60 years) with a parent with dementia will be matched (using propensity scores) on non-modifiable risk factors (age, gender and education) for dementia to participants of the Demin. Subsequently, multilevel analyses will be performed to examine the change in the LIBRA score and the individual health behaviours over time. In addition, possible confounding and interaction effects will be identified and corrected for in the analysis. We will calculate relative risks (RR) with 95% confidence intervals (CI) and use an alpha of 0.05 to test significance.

Adverse events

The risk classification of this intervention is considered negligible, since only information and health advice is provided. Serious adverse events as a result of the intervention are not expected, thus no data safety and monitoring board is installed. Potential participants are informed about possible adverse

events. For example dementia risk assessment may help raising the awareness of their susceptibility in order to motivate health behaviour change [27], however risk assessment could also have an unfavourable effect. Participants may become anxious about developing dementia and could experience more stress if they receive their health profile. Therefore, participants are clearly informed that the presence or absence of risk and protective factors is not a reassurance that they will develop dementia later in life. Furthermore, participants are informed that there is the possibility that unexpected medical findings can be found. In this case, participants receive a separate message in their personal inbox with the recommendation to contact their general practitioner to verify the results (hypertension, high cholesterol, renal dysfunction, diabetes) and discuss whether treatment is needed. Participants may consider online risk assessment as a privacy risk. In this study, all personal information is kept separately from the research data, and participants use a SMS-tan code to login in their personal account.

Ethics and dissemination

This study is approved by the Dutch ministry of Health, Welfare and Sport according to the Dutch Population Screening Act. All participants give informed consent to participate in this study, by signing an electronic informed consort form using SMS-tan (see **Supplementary file 4**). Authorship will be allocated using the guidelines for authorship defined by the International Committees of Medical Journal Editors (ICMJE) [53]. The results of the trial will be submitted to an international peer-reviewed journal and presented at national and international conferences.

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Competing interests None declared

Data availability The data collected during this study will be available from the corresponding author upon reasonable request.

Patient consent Obligatory

Ethics approval This study is approved by the Dutch ministry of Health, Welfare and Sport according to the population screening act. In addition, all participating memory clinics approved the study.

Supplementary files

Supplementary file 1 Measures Dementia Risk Assessment

Supplementary file 2 Overview of measurements at baseline and follow up

Supplementary file 3 Manuscript in submission

Supplementary file 4 Consent form model

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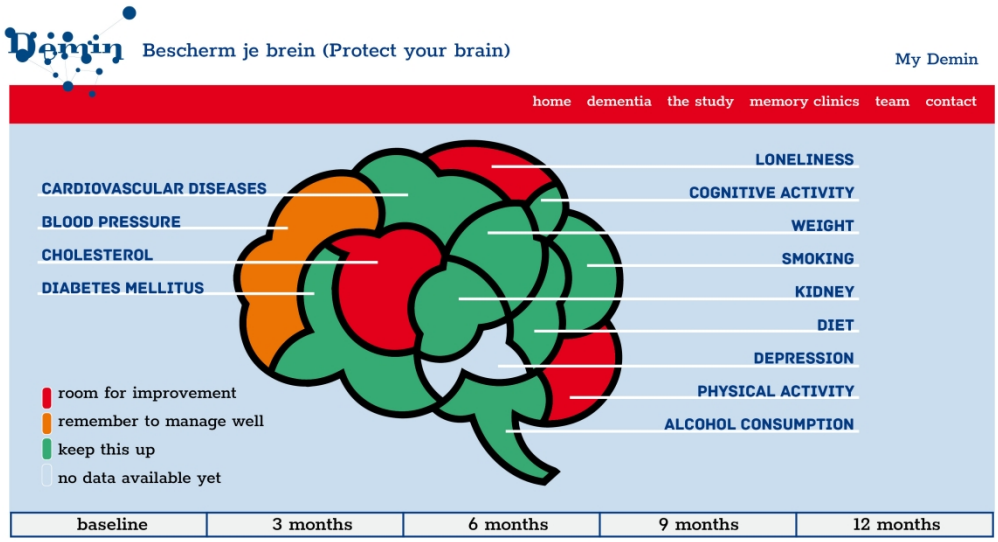

Figure 1. Example of a personal health profile

291x158mm (300 x 300 DPI)

Supplementary file 1: Measures Dementia Risk Assessment

Through the online questionnaire and physical examination, data on thirteen currently known protective (i.e. Mediterranean diet, low/moderate alcohol consumption, cognitive activity) and risk factors (i.e. physical inactivity, smoking, loneliness, cardiovascular diseases, hypertension, high cholesterol, diabetes mellitus, obesity, renal dysfunction, depression) for dementia are collected [1–3]. The measurements of these risk and protective factors are described below.

Protective factors

Mediterranean diet

The Mediterranean-DASH diet intervention for neurodegenerative delay (MIND) has shown to slow down cognitive decline [4] and to decrease the risk of developing AD [5]. Therefore, adherence to the MIND-diet is determined with a number of items of the Food Frequency Questionnaire (FFQ), which is a reliable and valid instrument to measure intake of a specified list of food items in the general populations [6,7]. The following healthy food groups of the MIND-diet were included in the questionnaire, such as vegetables (especially green leafy vegetables), nuts, berries, beans, whole grains, seafood, poultry, olive oil [4,5]. Also five unhealthy food groups of the MIND-diet including red meat, butter, cheese, sweets and fried/fast food were asked [4,5]. Based on the intake of the food groups, adherence to the MIND-diet is determined (0-14). A score of 14 represent good adherence to the MIND-diet *(See **Table 1** for the MIND-diet scoring table).*

Table 1. MIND-diet scoring table [5]

MIND components	Recommended quantity	Max score
Whole grains	≥ 3 serving spoons / day	1
Green leafy	≥ 6 serving spoons / week	1
Other vegetables	≥ 1 serving spoon / day	1
Berries (including other fruits)	≥ 2 portions / week *	1
Red Meats and products	< 4 portions / week	1

Fish	≥ 1 portion / week	1
Poultry	≥ 2 portions / week	1
Beans	> 3 serving spoons /week	1
Nuts	≥ 5 portions /week *	1
Fast/ fried food	< 1time / week	1
Butter, margarine	< 1 teaspoon/ day	1
Cheese	< 1 slice / week	1
Pastries, sweets	< 5 portions / week	1
Olive Oil (used as primary oil)	yes	1
Total score		**14**

** One portion is a handful of the given component*

Low/moderate alcohol consumption

Alcohol consumption was measured using the FFQ [6], including questions regarding the frequency of alcohol use (e.g. no consumption last month, 1 day per month, 2-3 days per month, 1 day per week, 2-3 days per week, 4-5 days per week, 6-7 days per week) and the average number of glasses of alcohol per day (range from zero to more than twelve) was asked. Subsequently, the average number of glasses per month was calculated in order to classify participants into: (i) non-alcohol consumers, (ii) low/moderate alcohol consumers or (iii) excessive alcohol consumers [8]. Participants adhere to the national recommendations for no to low/moderate alcohol consumption, if participants drink one glass or less alcohol per day on average, without binge drinking (more than three glasses alcohol on one day for females and more than four glasses alcohol on one day for males)) [9].

High cognitive activity

Cognitive activity is assessed with the leisure time section of the Cognitive Reserve Index questionnaire (CRIq) (22). CRIq aims to measure cognitive reserve (CR), which is based on education, working activity and leisure time activity. For this study we are interested in the current cognitive

activities of the participants. Therefore, cognitive activity is determined by measuring working activity and leisure time activity. The frequency of eighteen leisure time activity is asked (e.g. (i) never, (ii) less than once a month, (iii) once a month, (iv) once every 2 weeks, (v) several times a week). Subsequently, a leisure time cognitive activity score is calculated, ranging from to 18 to 108, where a score of 50 or higher represent high cognitive activity (based on results of a survey on the knowledge, beliefs and attitudes towards dementia risk reduction among the general population of Groningen, see Table 2 and 3).

Additionally, participants are asked if they have a paid job and if so how many hours they spend on their job per week. High cognitive activity is defined as (i) working at least 24 hours per week or (ii) a leisure time cognitive activity score of at least 50.

Table 2. Cognitive activity (leisure time) scores stratified for education level and having a paid job in a survey conducted among the general population in Groningen

Education level	**Work**	**Leisure time score**	
		mean(SD)	(min-max)
Low (n=105)	no work (n=75)	39.57 (11.16)	13 – 63
	work (n=30)	41.73 (11.12)	25 – 68
Middle (n=154)	no work (n=72)	47.03 (9.95)	26 – 76
	work (n=82)	45.20 (9.49)	25 – 64
High (n=390)	no work (n= 135)	51.93 (10.19)	18 – 75
	work (n=255)	48.32 (8.97)	23 – 74

Table 3. Cognitive activity (leisure time) scores stratified for education level and having a paid job in a survey conducted among the general population in Groningen (subgroup: 40 – 60 year old)

Education level	**Work**	**Leisure time score**	
		mean(SD)	(min-max)

Low (n=29)	no work (n=7)	39.71 (9.67)	21 – 49
	work (n=22)	40.50 (10.52)	25 – 58
Middle (n=68)	no work (n=9)	43. 89 (13.15)	26 – 66
	work (n=59)	46.34 (8.87)	25 – 64
High (n=140)	no work (n= 16)	50.56 (10.59)	37 – 69
	work (n=124)	49.91 (9.24)	23 – 74

Risk factors

Physical inactivity

Physical activity levels are determined using the Short Questionnaire to Asses Health enhancing physical activity (SQUASH), a self-reported questionnaire and commonly used instrument in the Netherlands to assess physical activity [10]. The SQUASH questionnaire has shown to be valid and reliable in measuring physical activity among the Dutch population [11–14]. The SQUASH questionnaire includes questions on multiple activities referring to an average week in the last month, including actively commuting (walking, cycling) to (voluntary) work or school, physical activity at (voluntary) work or school, household activities and leisure time activities, including walking, cycling, gardening and sports. Participants were asked to fill in how many days a week they engaged in the activities (frequency), the average time per day spent on each activity (hours and minutes; duration) and the intensity at which they did the activity (low, moderate, high) [10]. A standardized methodology was followed to calculate physical activity levels. Briefly, results from the SQUASH questionnaire are automatically converted to minutes per week spent in light (LPA) and moderate to vigorous (MVPA) intensity activities based on Metabolic Equivalent Tasks (METs) derived from the Ainsworth's compendium of physical activity [15]. Physical activity levels are divided into the following categories: 0 minutes MVPA per week, 0 to 149 minutes MVPA per week, 150 to 299 minutes MVPA per week and 300 minutes MVPA per week and more. Physical inactivity is defined as less than 150 minutes per week MVPA [16].

Additionally, the questionnaire contained information on sitting behaviour, which is divided into sitting during transportation, working hours, watching television or using the computer at home. Participants are asked to fill in the number of hours and minutes on an average day in the past seven days during the week and on an average day during the weekend. This is similar to the sitting measure of the International Physical Activity Questionnaire (IPAQ) which has shown to be valid and reliable [17]. Sitting time was divided into the following 4 categories: (i) less than 4 hours a day, (ii) 4 to 8 hours a day, (iii) 8 to 11 hours a day and (iv) at least 11 hours a day or more [18]. Prolonged sitting time was defined as sitting at least for 8 hours a day or more.

Participants are physically inactive if they (i) are sitting on average more than 8 hours a day, irrespective of the physical activity, or (ii) are sitting on average 4 hours or more a day and are less active than 150 minutes MVPA per week.

Smoking

Participants are asked three questions to measure smoking behaviour: (i) whether they have smoked in the past month, and (ii) whether they have smoked in the past, for at least one year [19]. Smoking behaviour is categorized into non-smoker, past smoker and current smoker. Current smokers are defined as people who reported smoking in the past month. Past smokers reported smoking for at least one year, but did not smoke in the past month.

Loneliness

Loneliness is measured using De Jong Gierveld Loneliness Scale , which is a reliable and valid instrument to measure emotional, social and overall loneliness [20]. Possible answers on this 6-item scale are: (i) yes!, (ii) yes, (iii) more or less, (iv), no, (v) no!. The overall loneliness score is calculated by counting the neutral and negative (“no!”, “no”, or “more or less”) answers on items 4, 5 and 6 (social loneliness score) and by counting the positive (“more or less””, “yes” or “yes!”) answers on items 1,2 and 3 (emotional loneliness score). Subsequently, the overall loneliness score is categorized into: (i) not lonely (0-1), (ii) moderate lonely (2-4), (iii) severe lonely (5-6). Loneliness is defined as an overall loneliness score of 2 or higher [20].

Cardiovascular diseases

Participants are asked whether they have suffered or still suffer from one of the following cardiovascular diseases: angina pectoris, myocardial infarction, transient ischemic attack (TIA), stroke or peripheral arterial diseases (yes/no). Presence of a cardiovascular disease is defined as having at least one of the above mentioned diseases.

Hypertension

Hypertension is determined based on the blood pressure measurement in which the systolic and diastolic blood pressure is measured both three times consecutively. The average of the second and the third measurement is used to determine the presence of hypertension. Hypertension is present: (i) if the systolic blood pressure is higher than 140 mmHg or diastolic blood pressure is higher than 90 mmHg [21], or (ii) if participants indicate that they receive medication (i.e. diuretics, beta blockers, ACE-inhibitors, angiotensin 2 antagonists and calcium antagonists) for their hypertension .

High cholesterol

High cholesterol is defined based on direct laboratory measurements using the fasting blood samples and self-reported questionnaires. High cholesterol is present if (i) the Low Density Lipoprotein (LDL) is higher than 2.5 mmol/l or (ii) the ratio of total cholesterol (TC) and High Density Lipoprotein (HDL) is higher than 8 mmol/l [22] or (iii) participants indicate that they receive medication (i.e. simvastinin, atorvastatin, rosuvastatin, pravastatin, ezetimib) to lower their cholesterol levels.

Diabetes Mellitus

The presence of diabetes mellitus (or impaired blood glucose levels) is based on direct laboratory measurements using the fasting blood samples and self-reported questionnaires. Diabetes Mellitus is defined as: (i) glucose (fasting capillary blood) of 7.0 mmol/l or higher, or (ii) glucose (fasting capillary blood) lower than 7.0 mmol/l accompanied by HbA1C levels higher than 53 mmol/mol [23].

HbA1C provides additional information on the average blood glucose levels during the previous month, while glucose may differ during the day [23].

Obesity

Body weight and body height are measured during physical examination in order to determine their Body Mass Index (BMI=kg/m^2)[24]. Obesity is present if BMI is 30 kg/m^2 or higher [25].

Renal dysfunction

The presence of renal dysfunction is based on direct laboratory measurements (serum creatinine levels) using the fasting blood samples and self-reported questionnaires [26]. Subsequently, the estimated glomerular filtration rate (eGFR) is calculated using the 2009 CKD-EPI creatinine equation [27,28] in order to determine participant's renal function [28]. Renal dysfunction is present if (i) eGFR is lower than 60 ml/min/1.73 m^2 [29], or (ii) participants indicate that they receive medical treatment for the established renal dysfunction.

Depression

The level of depressive symptoms is measured using the Centre for Epidemiologic Studies Depression scale (CES-D). The CES-D consists of 20 items and is a reliable and valid tool to measure the current level of depressive symptoms in the general population [30]. Answer options for each item are: rarely or none of the time (0), some or a little of the time (1), occasionally or a moderate amount of time (2), and most of all of the time (3). Total score varying from 0 to 60, indicates the level of depressive symptoms, a higher score reflects a higher level of depressive symptoms. Depression is defined as (i) having a score of 16 or higher [31], or (ii) participants indicate that they receive medical treatment for their depressive symptoms.

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Supplementary file 2. Overview of assessment measures at baseline and follow up

Table 1. Assessment measures at baseline and follow up					
	Baseline	**3 months**	**6 months**	**9 months**	**12months**
GENERAL INFORMATION					
Age, gender, ethnicity, education and postal code	Q				
Participation in the Lifelines cohort	Q				
Medical family history	Q				
Health literacy (S-TOFHLA, 3-items)	Q				
RISK AND PROTECTIVE FACTORS					
Smoking	Q	Q	Q	Q	Q
Physical inactivity (SQUASH, IPAQ sitting measure)	Q	Q	Q	Q	Q
Mediterranean diet (FFQ)	Q	Q	Q	Q	Q
Alcohol consumption (FFQ)	Q	Q	Q	Q	Q
High cognitive activity (CRIq adapted)	Q	Q	Q	Q	Q
Loneliness (de Jong Gierveld, 6-items)	Q	Q	Q	Q	Q
Cardiovascular diseases (CVD)	Q	Q	Q	Q	Q
Obesity (body weight, height)	Q+ PE	Q	Q	Q	Q+PE
Hypertension (SBD, DBP)	Q+PE	Q	Q	Q	Q+PE
High cholesterol (LDL, HDL, TC)	Q+BS	Q	Q	Q	Q+BS
Diabetes Mellitus[1] (glucose,	Q+BS	Q	Q	Q	Q+BS

HbA1C)					
Renal dysfunction (eGFR)	Q+BS	Q	Q	Q	Q+BS
Depression (CES-D)	Q	Q	Q	Q	Q
OTHER PARAMETERS					
Medical treatment of disease	Q	Q	Q	Q	Q
Motivation to change lifestyle (MCLHB-DRR)	Q	Q	Q	Q	Q
Stages of change	Q	Q	Q	Q	Q
Hearing problems	Q	Q	Q	Q	Q
Subjective stress (LDI)	Q				Q
Memory complaints	Q				
Quality of life (2 items of SF36, VAS-score)	Q				Q
Perceived living environment	Q				Q
Compliance lifestyle advice per individual health behaviour		Q	Q	Q	Q
Compliance advice contact with GP		Q	Q	Q	Q

SQUASH Short Questionnaire to Assess Health-enhancing physical activity, *IPAQ* International Physical Activity Questionnaire, *FFQ* Food Frequency Questionnaire, *CRIq* Cognitive Reserve Index questionnaire, *CVD* Cardiovascular diseases, *SBP* Systolic Blood Pressure, *DBP* Diastolic Blood Pressure, *HDL* high-density lipoproteins, *LDL* low-density lipoproteins, *TC* total cholesterol, *HbA1C* Hemoglobin A1C, *eGFR* estimated Glomerular Filtration Rate, *CES-D* Centre for Epidemiological Studies Depression Scale, *MCLHB-DRR* Motivation to Change Lifestyle and Health Behavior for Dementia Risk Reduction Scale, LDI Long-term Difficulties Inventory, *SF36* Short Form 36 items, *VAS* Visual Analogue Scale

Q: Online questionnaire; PE: Physical examination; BS: Blood sample

TITLE

Cross-cultural validation of the Motivation to Change Lifestyle and Health Behaviours for Dementia Risk Reduction scale in the Dutch general population

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ABSTRACT

BACKGROUND: This study aims to translate and validate the Motivation to Change Lifestyle and Health Behaviours for Dementia Risk Reduction (MCLHB-DRR) scale in the Dutch general population.

METHODS: A random sample of Dutch residents aged between 30 and 80 years old were invited to complete an online questionnaire including the translated MCLHB-DRR scale. Exploratory and confirmatory factor analyses (EFA and CFA) were conducted to assess construct validity. Cronbach's alpha was calculated to assess internal consistency.

RESULTS: 618 participants completed the questionnaire. EFA and Cronbach's alpha showed that four items were candidate for deletion. CFA confirmed that deleting these items led to an excellent fit (RMSEA = 0.043, CFI = 0.960, TLI = 0.951, $\chi^2/df = 2.130$). Cronbach's alpha ranged from 0.69 to 0.93, indicating good internal consistency.

CONCLUSION: The Dutch MCLHB-DRR scale demonstrated to have good validity to assess the health beliefs and attitudes towards dementia risk reduction.

KEY WORDS

Dementia risk reduction

Behaviour change

Lifestyle change

Cross-cultural validation

BACKGROUND

Dementia is a major public health concern for society. The prevalence of dementia increases rapidly, from 47 million cases worldwide in 2015 to an estimated 131 million cases in 2050 (1). The increasing number of dementia patients carries a high socioeconomic burden for society because of the associated rising health care costs and the burdensome effects of the disease on patients, their families and caregivers (2). The World Health Organization highlights dementia as a public health priority and advocates for action to decrease its social and economic burden (3).

The increase in the number of dementia patients is mainly attributable to population ageing, since age is the most important risk factor for dementia (1,4). In addition to non-modifiable risk factors for dementia like age and genetics, several studies suggested potential modifiable risk factors that are associated with dementia and in particular AD and vascular dementia (5-8). Recently, the evidence for these potential modifiable risk factors for dementia was summarized by Livingston et al. (2017) (8). They found that 35% of all dementia cases worldwide are attributable to nine modifiable risk factors and recommended to start interventions including more childhood education, promotion of exercise, reduction of smoking, maintaining social engagement and management of hypertension, diabetes, obesity, depression and hearing loss. It is estimated that these interventions might delay or prevent a third of all dementia cases (8).

Currently, there is no cure for dementia, so prevention of dementia is the key in fighting this disease. A diversity of multi-domain lifestyle interventions is conducted in elderly and people at risk for dementia in order to decrease the risk of developing dementia, including the

FINGER study, MAPT study, preDIVA study and HATICE trial (9-12). The aforementioned studies showed some evidence for effectiveness of a multi-domain approach to prevent elderly from cognitive decline, but further research is needed (13-15). Although behavioural change is crucial for dementia risk reduction, changing behaviour is complex and many factors are related to the chances for successfully altering behaviour according to different social cognitive theories and models (16-20). Measuring beliefs and attitudes towards lifestyle adaptations for dementia risk reduction may help to predict a person's willingness to change lifestyle and behaviour aiming to reduce one's risk of developing dementia.

The Motivation to Change Lifestyle and Health Behaviours for Dementia Risk Reduction (MCLHB-DRR) scale is developed in Australia and measures the beliefs and attitudes towards dementia and dementia risk reduction (21). The MCLHB-DRR scale was based on the Health Belief Model (HBM), since the HBM turned out to be the best-suited social cognitive model for dementia risk reduction (21). The HBM suggests that engagement in health-promoting behaviour is defined by a person's subjective risk assessment of getting a condition and how serious this condition and its consequences are, the perceived benefits and barriers of performing this behaviour, a stimulus to trigger this behaviour, the desire to achieve an outcome, and the confidence in one's ability to take action (22). The MCLHB-DRR scale consists of 27 items and includes all seven subscales of the HBM: perceived susceptibility, perceived severity, perceived benefits, perceived barriers, cues to action, general health motivation and self-efficacy. The MCLHB-DRR scale is considered to be valid and reliable in Australians aged 50 years and older (21). To our knowledge, the MCLHB-DRR scale has not yet been cross-culturally validated in any other language since its development in Australia.

There is currently no instrument available to measure attitudes and beliefs towards lifestyle and health behavioural changes for dementia risk reduction in the Netherlands. The MCLHB-DRR scale could be used to measure the attitudes and beliefs towards lifestyle adaptations for dementia risk reduction in the Dutch population. This induces the opportunity to use this scale in developing tailored interventions or education programs focused on lifestyle adjustments for dementia risk reduction. Therefore, the aim of the current study is to translate and validate the MCLHB-DRR scale in the Dutch general population aged between 30 and 80 years old.

METHODS

Study design and participants

MCLHB-DRR data were collected among a random sample of residents of the municipality of Groningen aged between 30 and 80 years old. From the 101,518 residents of the municipality of Groningen, 4,500 residents stratified for age (30-39, 40-49, 50-59, 60-69 and 70-80 years old) and gender (male, female) were randomly selected by a staff member of the municipality of Groningen. This staff member was not involved in the data collection nor data analyses of this study. The selected 4,500 residents were invited by mail to participate in an online survey about 'Lifestyle and dementia'. The translated MCLHB-DRR scale was the last part of this survey. The survey was built in Survey Monkey (SurveyMonkey Inc., San Mateo, California, VS, www.surveymonkey.com). In order to increase the response rate, participants were able to win a voucher of 20 Euros. Furthermore, participants were offered to receive the survey results on population level if they would finish the complete survey.

A pilot study was conducted to test the final version of the online survey 'Lifestyle and dementia'. A total of 25 people aged 30 to 80 years who were living outside the municipality of Groningen participated in the pilot study. They were recruited within the network of the research team members. Results of the pilot study did not lead to any changes in the final Dutch version of the MCLHB-DRR scale.

Questionnaire

The MCLHB-DRR scale is a self-reported questionnaire aiming to measure the attitudes and beliefs towards dementia and dementia risk reduction (21). The MCLHB-DRR scale consists of 27 items covering seven subscales: perceived susceptibility (4 items), perceived severity (5

items), perceived benefits (4 items), perceived barriers (4 items), cues to action (4 items), general health motivation (4 items) and self-efficacy (2 items). Items are answered on a 5 point Likert-scale, ranging from 'strongly disagree' (score = 1) to 'strongly agree' (score = 5) (21).

Scale translation

For the translation of the MCLHB-DRR scale, we used the method of Beaton et al. (2000) (23). Briefly, the MCLHB-DRR scale was translated into Dutch by three native Dutch translators, independently. Two of these translators were familiar with the concepts being examined in the questionnaire (the so-called informed translators). The third translator was not familiar with the content or concepts of the questionnaire (uninformed translator). All items, instructions and the response options of the questionnaire were translated. Subsequently, the three translated versions were synthesized to one Dutch version by the informed translators. The discrepancies between the three translated versions were discussed between the informed translators, taking the original questionnaire into account. Secondly, the synthesized Dutch version of the questionnaire was translated back into English by two independent native English speakers (uninformed translators). Both translators were not involved in the translation of the questionnaire from English to Dutch and were blinded to the original version of the questionnaire.

Afterwards all versions of the questionnaire, including the original version, the three translated versions, the synthesized Dutch version, the two back translations and all written reports about the decisions being made during the translation process were discussed by the informed translators. Special attention was paid to achieve semantic, idiomatic, experiential and conceptual equivalence between the source and target version of the questionnaire. After

a comprehensive review of all versions of the questionnaire, consensus about the pre-final version of the questionnaire was reached.

Finally, the two back translations were combined in the best possible way and this version was send to the developers of the original scale (21) to check whether the meaning of the translated items was equivalent to the meaning of the original items. Their feedback was discussed, resulting in a small change in the translation of item 20 and item 25. Afterwards, the Dutch final version of the MCLHB-DRR scale was established.

Statistical analysis

First, study population characteristics and characteristics of the MCLHB-DRR scale were calculated using descriptive statistics. Second, exploratory factor analysis (EFA) was performed. Maximum Likelihood estimation or Principal Axis Factoring was used depending on whether the data was roughly normally distributed or non-normally distributed, respectively. Oblique rotation was used as rotation method (delta (0)), which is taking into account correlations among factors. If the correlations between all factors were below 0.32, we changed to Varimax rotation (24). Items that did not have a correlation of 0.20 or higher with any of the other items were deleted immediately. Items with a high correlation (> 0.70) with any of the other items, were considered carefully. Items with a factor loading below 0.30 on any of the factors were deleted immediately. Deletion of an item was considered if the item did not load sufficiently on one of the factors (< 0.50) or if an item had a cross-loading greater than 0.30 (25).

Internal consistency of the subscales was evaluated by item-total correlations and Cronbach's alpha. Deletion of an item was considered when the item-total correlation of an item was below 0.30 (25). Cronbach's alpha values of 0.70 or higher were considered acceptable (26).

In addition, confirmatory factor analysis (CFA) was conducted. The following fit indices and their required levels were used to verify construct validity of the MCLHB-DRR scale: Root Mean Squared Error of Approximation (RMSEA) < 0.08 (moderate) and < 0.05 (excellent), Comparative Fit Index (CFI) and Tucker-Lewis Index (TLI) > 0.90 (moderate) and > 0.95 (excellent) and $\chi^2/df < 3.0$ (27,28).

EFA was performed using IBM SPSS Statistics software version 23 (SPSS Inc., Chicago, IL, USA). CFA was analysed using Stata version 13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.). Participants who did not complete the whole MCLHB-DRR scale were excluded from data analysis.

Ethics

The Medical Ethics Review Board of the UMCG concluded that this study was not subject to the Medical Research Involving Human Subjects Act. Respondents participated in this study voluntary. They could withdraw at any time without any consequence or penalty. Data were collected and analysed anonymously. All participants provided informed consent.

RESULTS

Participant recruitment

From the 4,500 selected potential participants, 621 participants completed the survey. The data of the 'cues to action' subscale of three participants were missing. These participants were excluded, leaving a total of 618 participants for data analysis.

Characteristics of the study population

The characteristics of the study population (n = 618) are presented in **Table 1**. The mean age of the participants was 57.3 ± 13.5 years and more than half of the participants were female (54%) and were married or had a registered partnership (54%). Most participants completed tertiary education (59%), followed by upper secondary education (24%), lower secondary education (14%) and elementary education (2%). About 58% of the participants were currently working. The percentages of participants knowing a relative with dementia or a non-relative with dementia were 45% and 21%, respectively.

Analysis of the psychometric characteristics of the MCLHB-DRR scale

Scale descriptives

The average MCLHB-DRR total scale score was 75.1 ± 11.1 (SD), ranging from 30 to 115. The total scale score was approximately normally distributed, although the scores were moderately leptokurtic (skewness = -0.394, kurtosis = 0.994). The mean subscale scores were 10.1 ± 2.7 (range = 4 to 18) for perceived susceptibility, 13.9 ± 3.7 (range = 5 to 25) for perceived severity, 12.6 ± 2.9 (range = 4 to 20) for perceived benefits, 8.0 ± 2.5 (range = 4 to 15) for perceived barriers, 10.2 ± 3.1 (range = 4 to 19) for cues to action, 14.5 ± 2.3 (range =

4 to 20) for general health motivation and 5.8 ± 1.7 (range = 2 to 10) for self-efficacy. All subscale scores were approximately normally distributed. Item response scores of the MCLHB-DRR scale ranged from 1.9 ± 0.8 (item 15) to 4.1 ± 0.7 (item 24).

Exploratory factor analysis

EFA analysis with extraction method Maximum Likelihood and Oblimin rotation was used to assess the number of factors, because the data were roughly normally distributed. First, a seven factor solution was evaluated as the original MCLHB-DRR scale consists of seven subscales. All items had an inter-item correlation greater than 0.20 with at least one of the other items. The correlation between item 1 and item 2 was 0.86 ($p < 0.001$), the correlation between item 1 and item 3 was 0.77 ($p < 0.001$) and the correlation between item 2 and item 3 was 0.82 ($p < 0.001$). Although these items had high inter-item correlations, they still measured something else ($r < 0.90$) and loaded on their intended factors. Therefore, none of these items was deleted. All other inter-item correlations did not exceed 0.70. The Bartlett's test of sphericity was significant, indicating that the data was adequate for factor analysis ($p < 0.001$). The first seven factors had eigenvalues greater than 1.00. The eigenvalues and the cumulative percentages of explained variance of the first seven factors in brackets were 5.86 (21.7%), 2.94 (32.6%), 2.52 (41.9%), 2.10 (49.7%), 1.56 (55.5%), 1.23 (60.0%) and 1.03 (63.9%), respectively. The scree plot also suggested a seven factor model.

Almost all items loaded on their intended subscales and did not have any significant cross-loadings. However, item 10 did not have a factor loading greater than 0.30 on any of the factors. Therefore, item 10 was deleted. Item 26 had a significant cross-loading (cross-loading = 0.37) on the perceived benefits subscale. Furthermore, items 4, 5, 7, 9, 13, 25 and 26 had factor loadings between 0.30 and 0.50 on their intended factors (**Table 2**). Inclusion of these

items was assessed in the next step by evaluating the internal consistency of their subscale. The inter-scale correlations between the subscale factors ranged from -0.13 to 0.51.

Internal consistency

Item-total correlation analysis showed that all items were positively correlated with the total MCLHB-DRR scale score. Item-total correlations ranged from 0.15 to 0.67. The item-total correlations of item 14 ($r = 0.28$), item 22 ($r = 0.15$), item 23 ($r = 0.26$) and item 24 ($r_s = 0.19$) were lower than 0.30. All other items had an item-total correlation above 0.30. Cronbach's alpha values were $\alpha = 0.86$ for perceived susceptibility, $\alpha = 0.76$ for perceived severity, $\alpha = 0.76$ for perceived benefits, $\alpha = 0.77$ for perceived barriers, $\alpha = 0.84$ for cues to action, $\alpha = 0.64$ for general health motivation and $\alpha = 0.81$ for self-efficacy, all indicating good internal consistency. Cronbach's alpha of the perceived susceptibility, perceived benefits and general health motivation subscales could be elevated by deleting an item. Items 4, 13 and 25 already had low factor loadings (factor loadings < 0.50) and were therefore eliminated. After deletion of these items, Cronbach's alpha values were $\alpha = 0.93$ for perceived susceptibility, $\alpha = 0.80$ for perceived benefits and $\alpha = 0.69$ for general health motivation. Cronbach's alpha of all subscales could not be raised any further after deleting these items (**Table 3**).

Confirmatory factor analysis

CFA with Maximum Likelihood method was conducted to explore the model fit of the MCLHB-DRR scale. A seven factor model with 23 items (excluding items 4, 10, 13 and 25) was evaluated with CFA (model 1). All fit indices were indicating an excellent fit (RMSEA = 0.043, CFI = 0.960, TLI = 0.951, $\chi^2/df = 2.130$) (**Table 4**). The factor loadings ranged from 0.395 to 0.978 and were all statistically significant (**Table 5**). A seven factor model including

all 27 items (model 2) showed a moderate fit (RMSEA = 0.053, CFI = 0.920, TLI = 0.907, $\chi^2/df = 2.743$), indicating model 1 had a better fit to the data than model 2.

DISCUSSION

We demonstrated that the Dutch version of the MCLHB-DRR scale consisting of 23 items is a valid instrument to measure the beliefs and attitudes towards lifestyle and health behavioural changes for dementia risk reduction in people aged between 30 and 80 years old. EFA showed that nearly all items loaded on their intended factors without cross-loadings. Cronbach's alpha varied from 0.69 to 0.93, indicating good internal consistency. CFA confirmed that a seven factor model including 23 items (without items 4, 10, 13 and 25) had an excellent fit to the data (RMSEA = 0.043, CFI = 0.960, TLI = 0.951, $\chi^2/df = 2.130$).

Items 4, 10, 13 and 25 had low factor loadings and were therefore not included in the final Dutch version of the instrument. This could possibly be explained by differences in knowledge of dementia and dementia prevention between residents of Australia and the Netherlands. Australia is leading in the field of dementia prevention with the world first publicly-funded dementia prevention program (29). This could lead to increased public awareness about dementia and the prevention of dementia in Australia. In general, the Australian population scored higher on all subscales of the MCLHB-DRR scale. Besides, differences in cultural beliefs about general health, health behaviours and the prestige of health professionals may play a role. Another possible explanation is the age difference between the Australian and Dutch study populations (21). The study population of the Australian study was 50 years and older whereas our population was between 30 and 80 years. People aged below 50 years might be less scared to develop dementia in the upcoming 10 years and might be less concerned about their health in comparison to people aged 50 years and over. However, our sensitivity analysis in which we only included people aged 50 years and over did not change our results in any way. Deficiencies in the translation process

could be a third explanation. The translation of item 10 slightly changed, as the part of the sentence 'may give me something that I never thought of' is not included in the Dutch translation.

Strengths and limitations

To our knowledge, this was the first study that validated the MCLHB-DRR scale in the Dutch general population. A major strength of the current study was the random sample, as the information letter was send to randomly selected residents of the municipality of Groningen. Another strength is the adequate sample size, consisting of a total number of 618 participants. Besides, we followed formal guidelines presented by Beaton et al. (2000) during the translation process (23).

This study also had certain limitations. The response rate of the current study was 14%, which is relatively low. However, we used several methods which have shown to increase the response rate to electronic surveys, such as a lottery to win a voucher, an offer to receive survey results on population level, a personalised invitation letter, an easily accessible link to the survey and a deadline to complete the survey (30,31). In our study, 59% of the participants completed tertiary education, which is higher than the percentage completing tertiary education in Dutch residents aged 45 years and over (26 %) (32). Therefore, the sample is not fully representative for the Dutch general population.

Recommendations for future research

First, assessing reliability and responsiveness of the Dutch MCLHB-DRR scale would be a valuable addition for future research. Second, a part of the study population might not be familiar with the health behaviours that decrease the risk of developing dementia. Future research could consider informing participants about these health behaviours before filling in

the MCLHB-DRR scale. Further research should also examine the association between the motivation to change lifestyle and health behaviours for dementia risk reduction and actually conducting this behaviour in daily life.

Implications

This scale can be useful in developing and evaluating interventions aimed at dementia risk reduction in various ways. Firstly, this instrument might help to predict people who will comply with an intervention program aimed at dementia prevention. Secondly, this instrument can be used in developing tailored interventions based on a person's motivations and beliefs. For example, if an individual scores low on the perceived benefits subscale, it would be convenient to educate this individual about how changing lifestyle and health behaviours could reduce its risk of dementia. Finally, assessing the beliefs towards lifestyle and health behavioural changes in the community population of the Netherlands may help to develop media campaigns or education programs focused on dementia prevention.

Conclusion

In summary, we have demonstrated that the translated and adapted Dutch version of the MCLHB-DRR scale consisting of 23 items is a valid instrument to assess beliefs and attitudes towards dementia and dementia risk reduction in the Dutch general population aged between 30 and 80 years old. The MCLHB-DRR scale can be used in the development and evaluation of lifestyle interventions and media campaigns aimed at dementia risk reduction.

LIST OF ABBREVIATIONS

MCLHB-DRR: Motivation to Change Lifestyle and Health Behaviours for Dementia Risk Reduction

EFA: Exploratory factor analyses

CFA: Confirmatory factor analyses

RMSEA: Root Mean Squared Error of Approximation

CFI: Comparative Fit Index

TLI: Tucker-Lewis Index

AD: Alzheimer's disease

HBM: Health Belief Model

SD: Standard deviation

DECLARATIONS

Ethics approval

The Medical Ethics Review Board of the UMCG concluded that this study was not subject to the Medical Research Involving Human Subjects Act. Respondents participated in this study voluntary. They could withdraw at any time without any consequence or penalty. Data were collected and analysed anonymously.

Patient consent All participants provided informed consent.

Availability of data and materials The datasets analysed during the current study are available from the corresponding author on reasonable request.

Competing interests None declared

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Authors' contributions All authors contributed to the design of the study. All co-authors read and approved the final manuscript.

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FIGURES AND TABLES

Table 1: Study population characteristics

Characteristic	All participants (N=618)[1]
Age, years (mean ± SD)	57.3 ± 13.5
Gender (% male)	281 (46%)
Marital status	
- Married/registered partnership	336 (54%)
- Domestic partnership	99 (16%)
- Living apart together (LAT)	23 (4%)
- Single	90 (15%)
- Widow/widower	20 (3%)
- Divorced	46 (7%)
- Others	4 (1%)
Education	
- Elementary	11 (2%)
- Lower secondary	88 (14%)
- Upper secondary	150 (24%)
- Tertiary	363 (59%)
- Others	6 (1%)
Working status (% currently working)	357 (58%)
Relative with dementia	276 (45%)
Non-relative with dementia	132 (21%)

[1] The numbers of participants (percentages) are shown unless otherwise stated.

Table 2: Exploratory factor analysis of the MCLHB-DRR scale (N=618, Maximum Likelihood with Oblimin rotation)

		Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 6	Factor 7
Q1	My chances of developing dementia are great	-0.02	**0.90**	0.00	-0.03	-0.03	0.03	0.04
Q2	I feel that my chances of developing dementia in the future are high	0.00	**0.97**	0.02	-0.04	-0.03	0.00	-0.00
Q3	There is a strong possibility that I will develop dementia	0.04	**0.86**	-0.03	0.01	0.02	-0.03	0.04
Q4	Within the next 10 years I will develop dementia	-0.04	**0.33**	0.07	0.25	0.07	-0.04	-0.12
Q5	The thought of dementia scares me	0.01	0.08	0.02	**0.49**	0.05	0.09	0.10
Q6	When I think about dementia my heart beats faster	-0.06	-0.00	0.10	**0.81**	0.01	-0.02	-0.04
Q7	My feelings about myself would change if I develop dementia	0.04	-0.01	-0.12	**0.43**	-0.01	0.03	0.10
Q8	When I think about dementia I feel nauseous	-0.03	-0.03	0.03	**0.80**	0.06	-0.05	-0.12
Q9	It would be more serious for me to develop dementia than if I developed other diseases	0.03	0.05	0.06	**0.45**	-0.04	0.00	-0.03
Q10	Information and advice from experts may give me something that I never thought of, and may reduce my chance of developing dementia	0.15	0.01	0.18	0.17	-0.09	0.01	0.20
Q11	Changing my lifestyle and health habits can help me reduce my chance of developing dementia	0.07	0.06	0.06	0.01	-0.04	-0.05	**0.77**
Q12	I have a lot to gain by changing my lifestyle and health behaviour	-0.03	0.03	0.08	0.01	0.05	-0.01	**0.77**
Q13	Adapting to a healthier lifestyle and behaviour would prevent dementia for me	0.13	-0.06	0.10	0.06	0.10	0.01	**0.38**
Q14	I am too busy to change my lifestyle and health habits	0.02	-0.03	0.00	-0.02	**0.61**	-0.05	-0.01
Q15	My financial situation does not allow me to change my lifestyle and behaviour	0.02	-0.02	0.06	0.05	**0.62**	0.05	-0.07
Q16	Family responsibilities make it hard for me to change my lifestyle and behaviour	-0.01	0.04	-0.09	-0.02	**0.78**	0.03	0.05
Q17	Changing lifestyle and behaviour interferes with my schedule	-0.02	-0.02	0.07	-0.00	**0.68**	-0.06	0.06

Q18 Being forgetful makes me think I have to change my lifestyle and behaviour	0.02	0.01	**0.68**	-0.02	0.05	0.01	-0.03
Q19 Having risk factor(s) for dementia makes me think I have to change my lifestyle and behaviour	0.01	0.03	**0.81**	-0.03	-0.01	0.01	0.04
Q20 Learning more about dementia from the media makes me think I have to change my lifestyle and behaviour	-0.01	-0.03	**0.71**	0.02	-0.03	0.03	0.17
Q21 Knowing family member(s) with dementia makes me think I have to change my lifestyle and behaviour	0.07	0.04	**0.64**	0.03	0.08	-0.02	0.00
Q22 Nothing is as important to me as good health	-0.03	-0.11	0.05	0.10	-0.08	**0.51**	-0.10
Q23 I often think about my health	0.00	-0.01	-0.03	-0.02	0.03	**0.85**	0.01
Q24 I think I have to pay attention to my own health	0.07	0.05	-0.05	-0.09	-0.01	**0.63**	-0.00
Q25 I am concerned about my health	-0.07	0.09	0.17	0.12	0.06	**0.32**	0.12
Q26 I am certain that I can change my lifestyle and behaviour so I can reduce the risk of developing dementia	**0.47**	0.03	0.16	-0.05	-0.03	0.03	**0.37**
Q27 I am able to make differences that will change the risk of developing dementia	**1.02**	-0.00	0.02	0.03	0.04	0.02	-0.07

The factor loadings greater than 0.30 are shown in bold. The boxes show the predicted subscales according to the results from Kim et al. 2014 (21).

Table 3: Internal consistency of the subscales

Subscale	Dutch MCLHB-DRR scale; N = 618				English MCLHB-DRR scale; N = 617			
	No. of items	Range of scores	Mean ± SD	α	No. of items	Range of scores	Mean ± SD	α
Perceived susceptibility	4	4-18	10.1±2.7	0.86[2]	4	4-19	NK	0.86
Perceived severity	5	5-25	13.9±3.7	0.76	5	5-25	NK	0.73
Perceived benefits	3[1]	3-15	9.1±2.3	0.76[3]	4	4-20	NK	0.69
Perceived barriers	4	4-15	8.0±2.5	0.77	4	4-20	NK	0.74
Cues to action	4	4-19	10.2±3.1	0.84	4	4-20	NK	0.68
General health motivation	4	4-20	14.5±2.3	0.64[4]	4	4-20	NK	0.61
Self-efficacy	2	2-10	5.8±1.7	0.81	2	2-10	NK	0.66

[1] Item 10 is deleted.

[2] Cronbach's alpha elevated to 0.93 if item 4 was deleted.

[3] Cronbach's alpha elevated to 0.80 if item 13 was deleted.

[4] Cronbach's alpha elevated to 0.69 if item 25 was deleted.

Abbreviations: α = Cronbach's alpha, MCLHB-DRR = Motivation to Change Lifestyle and Health Behaviours for Dementia Risk Reduction, NK = not known.

Table 4: Goodness of fit indexes of MCLHB-DRR models

Index	Dutch MCLHB-DRR scale (model 1)	Dutch MCLHB-DRR scale (model 2)	English MCLHB-DRR scale
RMSEA	0.043	0.053	0.047
CFI	0.960	0.920	0.920
TLI	0.951	0.907	NK
χ^2/df	2.130	2.743	2.380

Model 1 represents a seven factor model including 23 items (without items 4, 10, 13 and 25); model 2 represents a seven factor model including all 27 items.

Abbreviations: RMSEA = Root Mean Squared Error of Approximation, CFI = Comparative Fit Index, TLI = Tucker-Lewis Index, MCLHB-DRR = Motivation to Change Lifestyle and Health Behaviours for Dementia Risk Reduction, NK = not known.

Table 5: Confirmatory Factor Analysis report

Subscales	Item	Factor Loading
Perceived severity	Q1	0.896*
	Q2	0.953*
	Q3	0.858*
Perceived severity	Q5	0.573*
	Q6	0.842*
	Q7	0.395*
	Q8	0.753*
	Q9	0.487*
Perceived benefits	Q11	0.842*
	Q12	0.797*
Perceived barriers	Q14	0.627*
	Q15	0.617*
	Q16	0.734*
	Q17	0.719*
Cues to action	Q18	0.671*
	Q19	0.825*
	Q20	0.793*
	Q21	0.717*
General health motivation	Q22	0.562*
	Q23	0.815*
	Q24	0.612*
Self-efficacy	Q26	0.978*
	Q27	0.702*

Results are shown for model 1. *$p < 0.001$.

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01-02-2020 10:06:24

Beste Voornaam Achternaam,

Indien u wilt deelnemen aan dit onderzoek, vragen wij u dit toestemmingformulier door middel van een elektronische handtekening te ondertekenen. Hieronder vindt u de voorwaarde voor deelname aan dit onderzoek.

Wanneer u het toestemmingsformulier ondertekent verklaart u dat:

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- u genoeg tijd had om te beslissen of u wilt deelnemen.
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- u weet dat u op de hoogte gesteld kan worden van medische relevante bevindingen.

U geeft toestemming:

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– dat u in de toekomst opnieuw benaderd kan worden voor deelname aan aanvullend onderzoek.
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Met vriendelijke groet,

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Ik verklaar dat ik deze proefpersoon volledig heb geïnformeerd over het genoemde onderzoek.

Als er tijdens het onderzoek informatie bekend wordt die de toestemming van de proefpersoon zou kunnen beïnvloeden, dan breng ik hem/haar daarvan tijdig op de hoogte.

Naam hoofdonderzoeker:
Handtekening: Datum:
Tijdstip:

De deelnemer krijgt een volledige informatiebrief, samen met een kopie van het getekende toestemmingsformulier.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	All pages, no results
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	21
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	21
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1

Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	23
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	23
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6
Objectives	#7	Specific objectives or hypotheses	7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7-8
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8-9
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-16
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or	n/a

		improving / worsening disease)	
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	10
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	16-20
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11, 16
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8-9
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8-9
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a, one recruitment strategy per

			memory clinic
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10-11
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	19
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	22

Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a, low risk
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	20-21
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16-17
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	22
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	22
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	21
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16, 22
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a, low risk
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	21

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	21
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	21
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	21
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

The uptake and effectiveness of a tailor-made online lifestyle program targeting modifiable risk factors for dementia among middle-aged descendants of people with recently diagnosed dementia: study protocol of a cluster randomised controlled trial (Demin study)

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The uptake and effectiveness of a tailor-made online lifestyle program targeting modifiable risk factors for dementia among middle-aged descendants of people with recently diagnosed dementia: study protocol of a cluster randomised controlled trial (Demin study)

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ABSTRACT

Introduction Descendants of dementia patients have a higher risk to develop dementia. This study aims to investigate the uptake and effectiveness of an online tailor-made lifestyle program for Dementia Risk Reduction (DRR) among middle-aged descendants of people with recently diagnosed late-onset dementia.

Methods and analysis Demin is a cluster randomised controlled trial, aiming to include 21 memory clinics of which thirteen will be randomly allocated to the passive (poster and flyer in waiting room) and eight to the active recruitment strategy (additional personal invitation by members of the team of the memory clinic). We aim to recruit 378 participants (40-60 years) with a parent who is recently diagnosed with Alzheimer's Disease or Vascular Dementia at one of the participating memory clinics. All participants receive a dementia risk assessment (online questionnaire, physical examination and blood sample) and subsequently an online tailor-made lifestyle advice regarding protective (Mediterranean diet, low/moderate alcohol consumption, high cognitive activity) and risk factors (physical inactivity, smoking, loneliness, cardiovascular disease, hypertension, high cholesterol, diabetes, obesity, renal dysfunction, depression) for dementia. The primary outcome is the difference in uptake between the two recruitment strategies. Secondary outcomes are change(s) in 1) the Lifestyle for Brain Health (LIBRA) score, 2) individual health behaviours, 3) health beliefs and attitudes towards DRR and 4) compliance to the tailor-made lifestyle advice. Outcomes will be measured at 3, 6, 9 and 12 months after baseline. The effectiveness of this online tailor-made lifestyle program will be evaluated by comparing Demin participants to a matched control group (Lifelines cohort).

Ethics and dissemination This study has been approved by the Dutch Ministry of Health, Welfare and Sport according to the Population Screening Act. All participants have to give online informed consent using SMS-tan. Findings will be disseminated through peer-reviewed journals and (inter)national conferences.

Trial registration number NTR7434

ARTICLE SUMMARY

Strengths and limitations of this study

- This is the first multicentre trial that focuses on dementia risk reduction in middle-aged descendants of recently diagnosed patients with Alzheimer's disease or Vascular dementia.
- The program gives participants insight in their risk and protective factors for dementia and provides a tailor-made online lifestyle advice with regard to thirteen modifiable risk factors for dementia, taking the stages of (health behaviour) change into account.
- The application ensures the privacy of the participants by using SMS-tan for logging in their personal account and signing the electronic informed consent form.
- The web-based application (demin.nl) functions fully automatically, making it easy to implement the study in other memory clinics and settings.
- Changing health behaviour is difficult and it is unclear whether a tailor-made online lifestyle advice is sufficient to change health behaviour and to maintain a healthy lifestyle.

KEY WORDS

Dementia

Health behaviour

Risk reduction behaviour

Lifestyle

Middle aged

INTRODUCTION

Dementia is considered a major public health concern [1]. Due to the ageing population the number of dementia cases will increase substantially in the next decades. In 2015, more than 46 million people worldwide were affected by dementia and this number is expected to increase to 131 million by 2050 [2]. This rise in people with dementia carries a high economic and social burden for society [1]. In 2015, global costs of dementia reached 818 billion US dollars and will increase further [3]. Currently, no curative treatments are available. Therefore, prevention is a key element to counteract the dementia epidemic [4,5].

The most common types of dementia are Alzheimer's disease (AD) (60-70%) ,Vascular dementia (VD) (15-20%) or a combination of AD and VD (mixed dementia) [6–8]. The presence of a first-degree relative with AD doubles the risk for developing AD [9]. This increased risk has several reasons. Firstly, descendants of people with AD more often have a higher genetic predisposition for AD (e.g. carrier of the Apo lipoprotein E (APOE) ε4 allele) [9]. Secondly, high blood pressure, vascular diseases and other vascular risk factors (i.e. diabetes type 2, obesity, hypercholesterolemia) often cluster in families [10]. Lastly, psychosocial behaviour runs in the family and also affects health behaviour and lifestyle [11,12]. Not surprisingly, individuals with a parent who is recently diagnosed with AD or VD often worry about their own risk of developing dementia. Therefore, this life event (parental diagnosis of dementia) might encourage the willingness of individuals to change their health behaviour [13].

Parental family history has been associated with an increased risk of dementia independently of known genetic risk factors [9,14]. Therefore, a healthy lifestyle might be beneficial for individuals with a positive family history. Over the last decade, evidence of modifiable risk factors for dementia has been mounting [4,6,15]. The Lancet commission on dementia prevention, intervention and care demonstrated that 35% of the dementia cases is attributable to modifiable risk factors (i.e. less education, hearing loss, midlife hypertension, midlife obesity, smoking, depression, physical inactivity, social isolation and diabetes) and recommended to start interventions including more

childhood education, promotion of physical exercise, reduction of smoking, maintaining social engagement and management of hypertension, diabetes, obesity, depression and hearing loss [4,6,16]. Other major risk factors are hyperlipidaemia, coronary heart disease, renal dysfunction, Mediterranean diet and cognitive activity [15].

Only few studies examined the effectiveness of targeting these modifiable factors on cognitive decline and dementia incidence through a multi-domain intervention, such as the (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability) FINGER study [17], the (Prevention of Dementia by Intensive Vascular care) PreDIVA study [18] and the (The Multi-domain Alzheimer Preventive Trial) MAPT study [19]. These studies, with a follow-up varying from two to six years, found small or non-significant effects on cognition in older participants (e.g. >60 years) [17–19]. Starting multi-domain interventions earlier in life might be promising as cognitive decline begins already in midlife [20,21]. However, since dementia is mainly prevalent in the elderly, a long follow-up period of approximately 20 years would be required in order to determine the effectiveness of interventions on dementia incidence [20–22]. Furthermore, tailoring interventions improves the effectiveness of health behaviour change interventions [23]. Web-based interventions have the potential to support health behaviour change as there is the opportunity to tailor lifestyle advice [24–27]. They were especially effective when a theoretical basis or conceptual framework (e.g. Health belief model (HBM), Trans theoretical model (TTM), Theory of planned behaviour (TPB), I(integrated)-Change model [28–32]), behaviour change techniques (e.g. providing feedback on performance and information on the consequences of unhealthy behaviour) and several modes of delivery had been used [33].

The first challenge of health behaviour change interventions is to achieve a high level of uptake for screening (e.g. assessing risk and protective factors for dementia), reflecting the willingness to participate. A systematic review identified a large variation in uptake in health checks and lifestyle intervention programs [34], depending on the type of recruitment strategy. The two main types of strategies for recruitment are the active and passive recruitment strategy. Active recruitment involves a

personal invitation by the project staff and healthcare providers (e.g. proactive) and passive recruitment involves recruitment of participants through various channels such as flyers and advertisements (e.g. reactive) [35]. The most effective recruitment strategy is proactive referral from a healthcare provider, while displaying posters and flyers showed to be less effective [36]. Uptake also depends on other factors as described in social cognition models (e.g. knowledge, perceived susceptibility and severity, facilitators, benefits and barriers, and attitude towards such interventions) [28–32]. These factors are essential and useful to make a well-informed decision about dementia risk assessment, considering the possible benefits and harms. Therefore, information on dementia, the risk and protective factors for dementia, heritability, and how to tackle risk and protective factors for dementia are important factors in the development of a web-based intervention. A previous study showed that the majority of the Dutch general population is unaware of the relationship between modifiable risk factors and brain health, particularly regarding major cardiovascular risk factors (e.g. hypertension, hypercholesterolemia and coronary heart disease) [37]. Having a parent who is recently diagnosed with AD or VD could have led to an increased knowledge on dementia and risk perception [13]. Therefore, middle-aged descendants of recently diagnosed people with AD or VD might be receptive to assess their risk and motivated to adopt a healthier lifestyle as they just realized their (familial) risk [13,38].

To our knowledge, none of the health behaviour intervention studies were aimed at a specific group of middle-aged adults with increased risk for dementia due to their parental family history of dementia. Therefore, this study aims to investigate the uptake and effectiveness of a tailor-made online lifestyle program for dementia risk reduction among middle-aged descendants of recently diagnosed (in the last six months) people with AD or VD in the Netherlands. This will give insight in to what extent it is feasible to recruit middle-aged descendants of people with AD or VD at the memory clinics and whether these potential participants are willing to participate in a tailor-made online lifestyle program in order to reduce their dementia risk,

METHODS AND ANALYSIS

Study setting and design

This study is a pragmatic cluster randomized controlled trial (RCT), including 21 participating memory clinics in the Netherlands who are randomly allocated to a passive or active recruitment of participants. Memory clinics allocated to the active recruitment strategy invite potential participants face-to-face by a member of the team of the memory clinic to participate in the tailor-made online lifestyle program for dementia risk reduction (also called the Demin study), next to posters and flyers that are placed in the waiting room of the memory clinic. Memory clinics allocated to the passive recruitment strategy, do not invite potential participants pro-actively, but invite potential participants to participate in the Demin study by posters and flyers that are placed in the waiting room of the memory clinic.

Patients with AD or VD (or their caregivers) receive an envelope either at the registration desk of the memory clinic or after the consult of the patient (only with active recruitment). This envelope is addressed to the middle-aged descendants of patients with recently diagnosed AD or VD and includes a patient information form (PIF) with information about the content of the study, the advantages and disadvantages of study participation and how potential participants can participate. Potential participants (one family member per patient) are asked to register themselves (e.g. making an account) on the Demin website (www.demin.nl), by using the memory clinic specific login access code, which is reported on the front page of the PIF and represents the memory clinic in which the parent was diagnosed. The decision to participate is confirmed by the participants by signing the online informed consent form (electronic signature by using SMS-tan). After signing this form, individuals from both recruitment strategies are able to log in to their personalized website 'My Demin' and continue the intervention in an equal manner. The personalized website 'My Demin' is secured and only accessible for the participant by logging in with their personal e-mail address, password and SMS-tan code. 'My Demin' contains the following information: 1) My personal (account) information, 2) Message inbox, 3) My online questionnaires, 4) My personal health profile including online tailor-made lifestyle advice. After participants have completed the online questionnaire, they automatically receive a message with a request to make an appointment for physical examination including a fasting blood sample. Moreover, participants can invite siblings to participate in the study in 'My Demin'.

The functionalities provided by the Demin website are based on the literature and input we received from people with a parent with dementia (focus group discussions).

Randomization of memory clinics

To prevent contamination between the two recruitment strategies, randomization is performed at the level of the memory clinics. To enhance comparability between the intervention (participants of the active recruitment strategy) and control group (participants of the passive recruitment strategy), the memory clinics will be matched and randomised by a statistician, who is blind to the identity of the memory clinics and not involved in the study. Firstly, all participating memory clinics will be matched into pairs based on the following criteria: (i) number of newly diagnosed dementia (VD, AD or mixed dementia) patients seen per year (range vary from 60 to 350 patients per year) and (ii) the average social economic position (SEP) of the population living around the memory clinic (neighbourhood SEP), based on data from Statistics Netherlands [39]. Secondly, the matched memory clinics will be randomized (pairwise randomization) to an active recruitment strategy or passive recruitment strategy using a computer-generated random number list. As we expect a higher response rate in the active recruitment strategy group, we use an active : passive recruitment strategy ratio of 8:13 (see sample size calculations).

Study population

Eligible participants are middle-aged individuals (40-60 years old) with a parent who is recently (less than 6 months ago) diagnosed with AD or VD (or mixed dementia) at one of the participating memory clinics in the Netherlands (see acknowledgement). Individuals should provide informed consent, be able to fill out an online Dutch questionnaire. Pregnant women are excluded from participation.

Sample size calculations

The primary outcome measure is uptake, which is defined as the percentage of eligible individuals that signed the online informed consent form and completed baseline assessment (online questionnaire and physical examination and a fasting blood sample). In order to detect a difference of 20% in uptake

between the passive and active recruitment strategy (30% versus 50%), we need 94 participants in each group to achieve a power of 80% with alpha levels of 0.05 (total = 188 participants). To take cluster randomization into account, we use the formula 1+ ((n-1)*ICC) (inflation factor), where n is the average number of included participants per memory clinic and the ICC the Intra Class Correlation [40]. The ICC is unknown, but an ICC of 0.05 is a common value for cluster randomized controlled trials in hospitals [41]. The estimated average of included participants per memory clinic per year is n=15 using a passive recruitment strategy and n=25 using an active recruitment strategy, taking into account non-response. With unequal cluster sizes, 'n' is replaced by 'm', where m is the sum of $(M)^2/sum(M)$ $((15^2+25^2) / (15+25))$ [42]. This results in a sample size inflation factor of (1+ ((21.25-1)*0.05)= 2.01. Therefore, the total number of participants needed is 378 (2.01 * 188). In order to recruit 378 participants, we need 21 memory clinics, of which eight memory clinics (responsible for 189 included participants) will be allocated to the active recruitment strategy and thirteen memory clinics (responsible for 189 included participants) will be allocated to the passive recruitment strategy.

Demin website

The Demin website is available for everyone and provides information about dementia, heredity of dementia, risk and protective factors for dementia, and how to tackle potential risk factors for dementia. The health information will be provided by written text and in an audio-visual format, such as a spoken animation, to assure inclusion of participants with different levels of health literacy. [43].. According to the cognitive theory of multimedia learning (CTML), people process visual and auditory information through different channels [44,45]. It is known that health information provided by various channels, such as written text and spoken animations, improves information processing compared to information only provided through written text or spoken animations [44,45]. The instructions for registration (making an account, signing informed consent) are also provided as written text as visual screenshots representing the steps of the registration process.

Online tailor-made lifestyle program for dementia risk reduction

After participants give online informed consent, participants have access to the online tailor-made lifestyle program for dementia risk reduction, which consists of 1) a dementia risk assessment and 2) an online tailor-made lifestyle advice including a personal health profile targeting risk and protective factors for dementia.

1. Dementia risk assessment

The dementia risk assessment consists of filling out an online questionnaire (in 'My Demin') and physical examination, including a fasting blood sample, at one of the 21 participating memory clinics in order to determine whether risk and protective factors are present. In order to minimize the amount of missing data, validation and skip-and-fail rules were implemented in the online questionnaire. Furthermore, automatic reminders are sent to the participant if the online questionnaire was not filled in within two weeks. Physical examination will be conducted by the team of the local memory clinic and includes the following measurements: height (in cm) (SECA 222 stadiometer), body weight (in kg) without shoes (SECA 761 scale), waist- and hip circumference (in cm) (SECA 200 measuring tape), and three measurements of diastolic and systolic blood pressure (in mmHg) (Welch Allyn 'Spot Vital Signs' [46]). After physical examination, which takes approximately 15 minutes, a fasting blood sample (maximum of 21 ml) is taken for direct laboratory measurement of glucose, HbA1C, total cholesterol, High-density-lipoprotein (HDL), Low-density-lipoprotein (LDL), triglycerides and serum creatinine. The results of the physical examination (height, body weight, blood pressure, waist- and hip circumference) are sent to the researcher (J. Vrijsen) to check the entry of the results by the participants. The results of the direct laboratory measurements are sent to the medical doctor (E.M. Abma) of the University Medical Centre Groningen to check for deviating values.

Risk and protective factors for dementia

Through the online questionnaire and physical examination, data on thirteen currently known protective (i.e. Mediterranean diet, low/moderate alcohol consumption, cognitive activity) and risk factors (i.e. physical inactivity, smoking, loneliness, cardiovascular diseases, hypertension, high cholesterol, diabetes mellitus, obesity, renal dysfunction, depression) for dementia are collected

[6,15,47]. See **Table 1** for an overview of the assessment measures. The measurements of these risk and protective factors are described in **Supplementary file 1**.

Table 1. Assessment measures at baseline and follow up

	Baseline	**3 months**	**6 months**	**9 months**	**12months**
RISK AND PROTECTIVE FACTORS					
Smoking	Q	Q	Q	Q	Q
Physical inactivity (SQUASH, IPAQ)	Q	Q	Q	Q	Q
Mediterranean diet (FFQ)	Q	Q	Q	Q	Q
Alcohol consumption (FFQ)	Q	Q	Q	Q	Q
High cognitive activity (CRIq)	Q	Q	Q	Q	Q
Loneliness (de Jong Gierveld, 6-item)	Q	Q	Q	Q	Q
Cardiovascular diseases (CVD)	Q	Q	Q	Q	Q
Obesity (body weight, height)	Q+ PE	Q	Q	Q	Q+PE
Hypertension (SBD, DBP)	Q+PE	Q	Q	Q	Q+PE
High cholesterol (LDL, HDL, TC)	Q+FBS	Q	Q	Q	Q+FBS
Diabetes Mellitus (glucose, HbA1C)	Q+FBS	Q	Q	Q	Q+FBS
Renal dysfunction (eGFR)	Q+FBS	Q	Q	Q	Q+FBS
Depression (CES-D)	Q	Q	Q	Q	Q

SQUASH Short Questionnaire to Assess Health-enhancing physical activity, *IPAQ* International Physical Activity Questionnaire, *FFQ* Food Frequency Questionnaire, *CRIq* Cognitive Reserve Index questionnaire (adapted), *CVD* Cardiovascular diseases, *SBP* Systolic Blood Pressure, *DBP* Diastolic Blood Pressure, *HDL* high-density lipoproteins, *LDL* low-density lipoproteins, *TC* total cholesterol, *HbA1C* Haemoglobin A1C, *eGFR* estimated Glomerular Filtration Rate, *CES-D* Centre for Epidemiological Studies Depression Scale

Q: Online questionnaire, PE: Physical examination, FBS: Fasting blood sample

2a. Personal health profile

After completion of the baseline dementia risk assessment (including the data entry of the physical examination and laboratory measurements), a personal health profile is automatically provided in the personal account of the participants (My Demin). The personal health profile gives an overview of the presence of the risk and protective factors for dementia. According to the Lifestyle for Brain Health (LIBRA) score, each risk and protective factor [47–49] is categorized into one of the following categories: 1) room for improvement, 2) remember to manage well, 3) keep this up (see **Table 2**). The "Keep this up" category represent factors that participants are currently managing well or diseases they do not have. The "Room for improvement" category represents the factors that could be improved by health behaviour change (e.g. quit smoking, become more physical active, change diet, drink less alcohol). The category "Remember to manage well" is assigned when a risk factor (i.e. cardiovascular disease, hypertension, high cholesterol, diabetes mellitus, renal dysfunction and depression) is present, but the disease is managed well as participants have regular meetings with their general practitioner for disease control (diabetes mellitus) or use medication for disease management (cardiovascular disease, hypertension, high cholesterol, renal dysfunction and depression) (see **Figure 1**).

[INSERT FIGURE 1 ABOUT HERE]

299 **Table 2.** Definition for the 3 categories in the personal health profile at baseline

Modifiable risk factors	Keep this up	Remember to manage well	Room for improvement
Diet	MIND-diet score = 14 points	n.a.	MIND-diet score < 14 points
Alcohol consumption	Average number of units of alcohol per week ≤ 7 and number of units per day is: ≤ 3 for women or ≤ 4 for men	n.a.	Average number of units of alcohol per week > 7 or number of units per day is: > 3 for women or > 4 for men
Cognitive activity	paid working hours ≥ 24 or CRIq score ≥ 50	n.a.	paid working hours < 24 and CRIq score < 50
Physical activity	(MVPA / week ≥ 150 and Sitting time ≤ 8 hours / day) or (MVPA / week < 150 and sitting time < 4 hours / day)	n.a.	(Sitting time > 8 hours / day) or (Sitting time ≥ 4 hours / day and MVPA / week < 150)
Smoking	Past or never smoker	n.a.	Current smoker
Loneliness	De Jong Gierveld score < 2	n.a.	De Jong Gierveld score ≥ 2
Cardiovascular diseases (CVD)	no CVD	at least one CVD and receives medical treatment	at least one CVD and no medical treatment
Weight	BMI ≥ 18.5 and BMI < 25.0	n.a.	BMI < 18.5 or BMI ≥ 25.0

Blood pressure	DBP < 90 mmHg and SBP < 140 and no medical treatment	DBP < 90 mmHg and SBP < 140 and medical treatment	DBP ≥ 90 mmHg or SBP ≥ 140 mmHg
Cholesterol	(LDL ≤ 2.5 mmol/l and TC/HDL ≤ 8) and no medical treatment	(LDL ≤ 2.5 mmol/l and TC/HDL ≤ 8) and medical treatment	LDL > 2.5 mmol/l or TC/HDL > 8
Diabetes Mellitus	glucose < 7.0 mmol and HbA1C ≤ 53 mmol/mol	(HbA1C ≤ 53 mmol/mol and medical treatment) or (glucose < 7.0 mmol and HbA1C > 53 mmol/mol and medical treatment)	(HbA1C > 53 mmol/mol and no medical treatment) or (glucose ≥ 7.0 mmol and HbA1C > 53 mmol/mol) or (glucose ≥ 7.0 mmol and HbA1C ≤ 53 mmol/mol and no medical treatment)
Kidney	eGFR ≥ 60 ml/min/1.73 m^2	eGFR < 60 ml/min/1.73 m^2 and medical treatment	eGFR < 60 ml/min/1.73 m^2 and no medical treatment
Depression	CES-D < 16 points	CES-D ≥ 16 points and medical treatment	CES-D ≥ 16 points and no medical treatment

MIND-diet Mediterranean-DASH Diet Intervention for Neurodegenerative Delay, *CRIq* Cognitive Reserve Index questionnaire, *MVPA* Moderate to vigorous physical activity, CVD Cardiovascular diseases, *BMI* Body mass index, *DBP* diastolic blood pressure, *SBP* systolic blood pressure, *LDL* low-

density lipoproteins, *TC* total cholesterol, *HDL* high-density lipoproteins, *HbA1C* Haemoglobin A1C, *eGFR* estimated Glomerular Filtration Rate, *CES-D* Centre for Epidemiological Studies Depression Scale

2b. Tailor-made online lifestyle advice for dementia risk reduction

Participants also receive an online tailor-made lifestyle advice targeting risk factors associated with dementia and following the Dutch guidelines for a healthy diet, alcohol consumption, physical activity, diabetes mellitus, renal dysfunction and cardiovascular health including cholesterol levels and BMI [50–54]. For each risk and protective factor, information is given about (i) the norm (cut-off point for not having this risk factor), (ii) the association between the risk factor and dementia and (iii) lifestyle advice how to tackle this factor. The online lifestyle advice was tailored to the participants based on (i) the presence of risk factors, (ii) the strength of the association between the risk factors and dementia [15,47] and (iii) the stages of change of the health behaviour related risk factors (physical inactivity, diet, alcohol consumption, smoking behaviour, cognitive activity, social activity). The stages of change are determined by asking "Which statement fits best for you?", where each answer option reflects one of the following stages of change: pre-contemplation, contemplation, preparation, action and maintenance [29]. It is known that participants who are in the preparation and action stage are more willing to change their health behaviour, therefore lifestyle advice for these factors are given first [29].

In case medically relevant findings are found, including untreated diabetes mellitus (glucose ≥ 7.0 mmol/l or (glucose ≥ 6.1 mmol/l and HbA1C > 53 mmol/mol)), untreated renal dysfunction (estimated Glomerular Filtration Rate (eGFR) ≤ 60 ml/min/1.73 m2) and increased risk for developing cardiovascular diseases (CVD) (CVD risk ≥ 10% according to the Dutch SCORE formula [54]), participants receive, in addition to the online tailor-made lifestyle advice, a separate message in their personal inbox with the recommendation to contact their general practitioner to verify the results and discuss whether treatment is needed.

Outcome measures and measurements

Participants are invited to fill in the online questionnaire at baseline and four times (3, 6, 9 and 12 months after baseline measurement) during one year follow-up. Physical examination, including the fasting blood sample for direct laboratory measurements, is only done at baseline and 12 months after

baseline measurement (see **Supplementary file 2**). Data from the online questionnaires and physical examination are stored automatically in an electronic Case Report Form (eCRF) data management program, which is only accessible by the researchers involved in this study. Data from the direct laboratory measurement are entered manually in the electronic Case Report Form (eCRF) data management program. Every month, memory clinics are requested to provide information about 1) the number of eligible participants (e.g. new cases of AD and VD), 2) the number of envelopes that are given away, and 3) any difficulties with the recruitment of participants. In order to keep participating memory clinics involved in the study, every three months newsletters are sent around and memory clinics are contacted monthly to evaluate the uptake.

Primary outcome

The primary outcome is the difference in uptake (e.g. the percentage of eligible people that signed the online informed consent form and completed risk assessment of the total number of eligible people) between the active and passive recruitment strategy. The total number of eligible people in each recruitment group (active versus passive) are based on the number of new cases of AD or VD in all memory clinics during the recruitment period, assuming an average of one child per dementia patient receiving the envelope with the PIF including a login access number.

Secondary outcomes

Secondary outcomes include:

1) The change in Lifestyle for Brain Health (LIBRA) score. The LIBRA score has been validated among individuals in midlife and reflects an individual's potential to reduce their risk on developing late-onset dementia [47]. The LIBRA score consists of twelve currently known protective (i.e. Mediterranean diet, low/moderate alcohol consumption, cognitive activity) and risk factors (i.e. physical inactivity, smoking, cardiovascular diseases, hypertension, high cholesterol, diabetes mellitus, obesity, renal dysfunction, depression) for dementia (13, 14,31) and ranges from -5.9 (low risk for developing dementia) to 12.7 (high risk for developing dementia).

A one point increase in the LIBRA score is associated with a 19% higher risk for dementia [47,55]. The definitions and corresponding scores for the three protective and ten risk factors for dementia are described in **Table 3**.

Table 3. Definition of risk and protective factors for dementia in the LIBRA score and corresponding scores

Modifiable risk factors		**Definition**	**Score**
Protective factors			
1	High cognitive activity	Score ≥ 50 points on the Cognitive Reserve Index questionnaire (leisure time activities) (CRIq) or hours of paid work ≥ 24 hours	-3.2
2	Mediterranean diet	MIND-diet score (0-14) = 14 points	-1.7
3	Low/moderate alcohol consumption	Average number of glasses of alcohol a week ≤ 7 and number of glasses a day is: ≤ 3 glasses for women (no binge drinking) ≤ 4 glasses for men (no binge drinking)	-1.0
Risk factors			
4	Cardiovascular diseases (CVD)	Presence of at least one of the follow diseases: history of angina pectoris, myocardial infarction, transient ischemic attacks, stroke or peripheral arterial diseases	+1.0
5	Physical inactivity	Not fulfilling Dutch Norm for Physical activity defined as ≥ 150 min/week physical activity of moderate to vigorous intensity, measured with the SQUASH questionnaire	+1.1
6	Renal dysfunction	Estimated glomerular filtration rate ≤ 60 ml/min/1.73	+1.1
7	Diabetes Mellitus	Glucose (capillary blood) > 7.0 mmol/l or HbA1c > 53 mmol/mol	+1.3
8	High cholesterol	LDL > 2.5 mmol/l or TC/HDL ≥ 8	+1.4
9	Smoking	Current smoker	+1.5

10	Obesity	BMI ≥ 30	+1.6
11	Hypertension	SBP > 140 mmHg or DBP > 90 mmHg	+1.6
12	Depression	Score ≥ 16 points on the Centre for Epidemiologic Studies Depression scale (CES-D)	+2.1

LDL low-density lipoproteins*, TC* total cholesterol, *HDL* high-density lipoproteins*, BMI* Body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

2) The change in the individual health behaviours, including physical activity (minutes of MVPA per week), diet (MIND-diet score; 0-14), alcohol consumption (number of glasses of alcohol per week), smoking behaviour (current smoker (yes/no) and number of cigarettes/cigars a day), cognitive activity (leisure-time cognitive activity score and number of hours paid work), loneliness (overall loneliness score; 0-6) and social activity (number of contacts per two weeks) and their stage of change over time. The stages of change are categorized into pre-contemplation (1), contemplation (2), preparation (3), action (4) and maintenance (5) [29].

3) Changes in beliefs and attitudes with regard to dementia risk reduction are measured using the Motivation to Change Lifestyle and Health Behaviour for Dementia Risk Reduction Scale (MCLHB-DRR scale) [56,57]. The MCLHB-DRR scale is based on the Health Belief Model [28], which explains health-related behaviours. Seven subscales of the Health Belief Model were included: perceived susceptibility, perceived severity, perceived benefits, perceives barriers, cues to action, general health motivation and self-efficacy. Participants are asked to rate all items on a 5-point Likert scale, ranging from strongly disagree (score=1) to strongly agree (score=5). A minimum score of 23 and a maximum score of 115 can be achieved. A higher score reflects a higher motivation to change their lifestyle and health behaviour for dementia risk reduction. The Dutch version of the MCLHB-DRR scale, consisting of 23 items, has shown to be valid in the Dutch general population aged between 30 and 80 years old [58].

4) Percentage of participants that indicated in the questionnaire that they have followed up the tailor-made online lifestyle advice ("On what risk factors did you receive lifestyle advice?" and "Did you follow up the tailor-made lifestyle advice since the last questionnaire (with regard to [risk factor])"? , but also the percentage of participants that indicated that they have followed up the advice to consult their General Practitioner ("Did you have contact with your general practitioner after receiving feedback on the risk and protective factors?").

Statistical analyses

First, descriptive characteristics will be explored. The difference in uptake between the two recruitment strategies will be examined using multilevel logistic regression analyses in order to correct for clustering at memory clinic level. We will calculate the percentage with the corresponding 95% confidence interval (CI) and use an alpha of 0.05 to test statistical significance.

The effectiveness of the online tailor-made lifestyle program for dementia risk reduction will be determined by, firstly comparing the change in LIBRA score, the individual risk factors and the MCLHB-DRR score between the active and passive recruitment strategy, and secondly comparing participants of the Demin study (active and passive recruitment strategy) to a control group consisting of Lifelines participants (large population-based cohort study (n> 167.000)) (www.lifelines.nl)[59] in outcome. Lifelines participants (age 40 – 60 years) with a parent with dementia will be matched (using propensity scores) on non-modifiable risk factors (age, gender and education) for dementia to participants of the Demin. Subsequently, multilevel analyses will be performed to examine the change in the LIBRA score and the individual health behaviours over time. In addition, possible confounding and interaction effects will be identified and corrected for in the analysis. We will calculate relative risks (RR) with 95% confidence intervals (CI) and use an alpha of 0.05 to test significance.

Adverse events

The risk classification of this intervention is considered negligible, since only information and health advice is provided. Serious adverse events as a result of the intervention are not expected, thus no data safety and monitoring board is installed. Potential participants are informed about possible adverse

events. For example dementia risk assessment may help raising the awareness of their susceptibility in order to motivate health behaviour change [28], however risk assessment could also have an unfavourable effect. Participants may become anxious about developing dementia and could experience more stress if they receive their health profile. Therefore, participants are clearly informed that the presence or absence of risk and protective factors is not a reassurance that they will develop dementia later in life. Furthermore, participants are informed that there is the possibility that unexpected medical findings can be found. In this case, participants receive a separate message in their personal inbox with the recommendation to contact their general practitioner to verify the results (hypertension, high cholesterol, renal dysfunction, diabetes) and discuss whether treatment is needed. Participants may consider online risk assessment as a privacy risk. In this study, all personal information is kept separately from the research data, and participants use a SMS-tan code to login in their personal account.

Patient and Public Involvement

Descendants of people with dementia were involved in the development of the Demin website. We assessed the knowledge, beliefs and attitudes towards dementia and dementia risk reduction among descendants of people with dementia (focus group discussions). The results of the focus group discussions were used to develop the Demin website in order to improve the participant recruitment and encourage health behaviour change among participants.

Ethics and dissemination

This study is approved by the Dutch ministry of Health, Welfare and Sport according to the Dutch Population Screening Act. Research which is considered to be Population Screening on the ground of the Population Screening Act, for which ministerial approval is required, does not have to be assessed on the basis of the Medical Research Involving Human Subjects Act [60]. Population screening is defined as 'medical research in persons carried out on an entire population or a category thereof aimed at the detection of certain types of disease or certain risk indicators for the benefit of the participating subjects'[61]. This project focuses on the attenuations of risk factors for dementia. Since these risk

factors are merely lifestyle factors, a positive impact beyond dementia may be expected. Due to a healthy lifestyle more healthy life years are added to people's lives, which may ultimately increase the risk on dementia as age is an important risk factor for dementia. This research is conducted in accordance to the international ethical guidelines [62].

All participants give informed consent to participate in this study, by signing an electronic informed consort form using SMS-tan (see **Supplementary file 3**). Authorship will be allocated using the guidelines for authorship defined by the International Committees of Medical Journal Editors (ICMJE) [63]. The results of the trial will be submitted to an international peer-reviewed journal and presented at national and international conferences.

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Competing interests None declared

Data availability The data collected during this study will be available from the corresponding author upon reasonable request. This study aims to include data from 378 middle-aged participants recruited through participating memory clinics in the Netherlands. The final dataset will include data on physical examination, laboratory data from fasting blood samples and self-reported data including demographic characteristics, health and health behaviour. We will make the data and associated documentation available to users conditional on a data-sharing agreement that provides for: (1) a commitment to using the data only for research purposes, (2) a commitment to securing the data using appropriate computer technology, and (3) a commitment to destroying or returning the data after analyses are completed.

Patient consent Obligatory

Ethics approval This study is approved by the Dutch ministry of Health, Welfare and Sport according to the population screening act. In addition, all participating memory clinics approved the study.

Supplementary files

Supplementary file 1 Measures Dementia Risk Assessment

Supplementary file 2 Overview of measurements at baseline and follow up

Supplementary file 3 Consent form model

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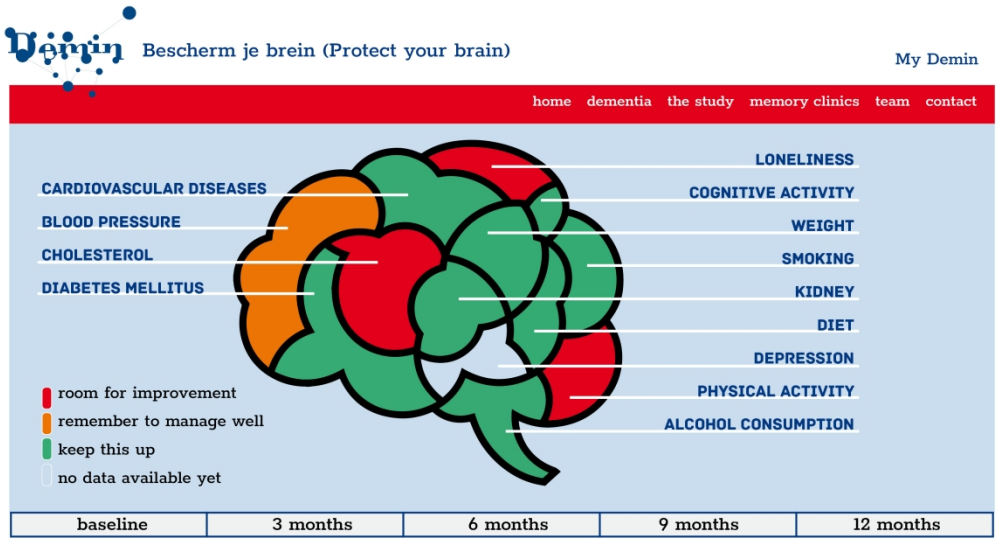

Figure 1. Example of a personal health profile

291x158mm (300 x 300 DPI)

Supplementary file 1: Measures Dementia Risk Assessment

Through the online questionnaire and physical examination, data on thirteen currently known protective (i.e. Mediterranean diet, low/moderate alcohol consumption, cognitive activity) and risk factors (i.e. physical inactivity, smoking, loneliness, cardiovascular diseases, hypertension, high cholesterol, diabetes mellitus, obesity, renal dysfunction, depression) for dementia are collected [1–3]. The measurements of these risk and protective factors are described below.

Protective factors

Mediterranean diet

The Mediterranean-DASH diet intervention for neurodegenerative delay (MIND) has shown to slow down cognitive decline [4] and to decrease the risk of developing AD [5]. Therefore, adherence to the MIND-diet is determined with a number of items of the Food Frequency Questionnaire (FFQ), which is a reliable and valid instrument to measure intake of a specified list of food items in the general populations [6,7]. The following healthy food groups of the MIND-diet were included in the questionnaire, such as vegetables (especially green leafy vegetables), nuts, berries, beans, whole grains, seafood, poultry, olive oil [4,5]. Also five unhealthy food groups of the MIND-diet including red meat, butter, cheese, sweets and fried/fast food were asked [4,5]. Based on the intake of the food groups, adherence to the MIND-diet is determined (0-14). A score of 14 represent good adherence to the MIND-diet *(See **Table 1** for the MIND-diet scoring table).*

Table 1. MIND-diet scoring table [5]

MIND components	Recommended quantity	Max score
Whole grains	≥ 3 serving spoons / day	1
Green leafy	≥ 6 serving spoons / week	1
Other vegetables	≥ 1 serving spoon / day	1
Berries (including other fruits)	≥ 2 portions / week *	1
Red Meats and products	< 4 portions / week	1

Fish	≥ 1 portion / week	1
Poultry	≥ 2 portions / week	1
Beans	> 3 serving spoons /week	1
Nuts	≥ 5 portions /week *	1
Fast/ fried food	< 1time / week	1
Butter, margarine	< 1 teaspoon/ day	1
Cheese	< 1 slice / week	1
Pastries, sweets	< 5 portions / week	1
Olive Oil (used as primary oil)	yes	1
Total score		**14**

** One portion is a handful of the given component*

Low/moderate alcohol consumption

Alcohol consumption was measured using the FFQ [6], including questions regarding the frequency of alcohol use (e.g. no consumption last month, 1 day per month, 2-3 days per month, 1 day per week, 2-3 days per week, 4-5 days per week, 6-7 days per week) and the average number of glasses of alcohol per day (range from zero to more than twelve) was asked. Subsequently, the average number of glasses per month was calculated in order to classify participants into: (i) non-alcohol consumers, (ii) low/moderate alcohol consumers or (iii) excessive alcohol consumers [8]. Participants adhere to the national recommendations for no to low/moderate alcohol consumption, if participants drink one glass or less alcohol per day on average, without binge drinking (more than three glasses alcohol on one day for females and more than four glasses alcohol on one day for males)) [9].

High cognitive activity

Cognitive activity is assessed with the leisure time section of the Cognitive Reserve Index questionnaire (CRIq) (22). CRIq aims to measure cognitive reserve (CR), which is based on education, working activity and leisure time activity. For this study we are interested in the current cognitive

activities of the participants. Therefore, cognitive activity is determined by measuring working activity and leisure time activity. The frequency of eighteen leisure time activity is asked (e.g. (i) never, (ii) less than once a month, (iii) once a month, (iv) once every 2 weeks, (v) several times a week). Subsequently, a leisure time cognitive activity score is calculated, ranging from to 18 to 108, where a score of 50 or higher represent high cognitive activity (based on results of a survey on the knowledge, beliefs and attitudes towards dementia risk reduction among the general population of Groningen, see Table 2 and 3).

Additionally, participants are asked if they have a paid job and if so how many hours they spend on their job per week. High cognitive activity is defined as (i) working at least 24 hours per week or (ii) a leisure time cognitive activity score of at least 50.

Table 2. Cognitive activity (leisure time) scores stratified for education level and having a paid job in a survey conducted among the general population in Groningen

Education level	**Work**	**Leisure time score**	
		mean(SD)	(min-max)
Low (n=105)	no work (n=75)	39.57 (11.16)	13 – 63
	work (n=30)	41.73 (11.12)	25 – 68
Middle (n=154)	no work (n=72)	47.03 (9.95)	26 – 76
	work (n=82)	45.20 (9.49)	25 – 64
High (n=390)	no work (n= 135)	51.93 (10.19)	18 – 75
	work (n=255)	48.32 (8.97)	23 – 74

Table 3. Cognitive activity (leisure time) scores stratified for education level and having a paid job in a survey conducted among the general population in Groningen (subgroup: 40 – 60 year old)

Education level	**Work**	**Leisure time score**	
		mean(SD)	(min-max)

Low (n=29)	no work (n=7)	39.71 (9.67)	21 – 49
	work (n=22)	40.50 (10.52)	25 – 58
Middle (n=68)	no work (n=9)	43. 89 (13.15)	26 – 66
	work (n=59)	46.34 (8.87)	25 – 64
High (n=140)	no work (n= 16)	50.56 (10.59)	37 – 69
	work (n=124)	49.91 (9.24)	23 – 74

Risk factors

Physical inactivity

Physical activity levels are determined using the Short Questionnaire to Asses Health enhancing physical activity (SQUASH), a self-reported questionnaire and commonly used instrument in the Netherlands to assess physical activity [10]. The SQUASH questionnaire has shown to be valid and reliable in measuring physical activity among the Dutch population [11–14]. The SQUASH questionnaire includes questions on multiple activities referring to an average week in the last month, including actively commuting (walking, cycling) to (voluntary) work or school, physical activity at (voluntary) work or school, household activities and leisure time activities, including walking, cycling, gardening and sports. Participants were asked to fill in how many days a week they engaged in the activities (frequency), the average time per day spent on each activity (hours and minutes; duration) and the intensity at which they did the activity (low, moderate, high) [10]. A standardized methodology was followed to calculate physical activity levels. Briefly, results from the SQUASH questionnaire are automatically converted to minutes per week spent in light (LPA) and moderate to vigorous (MVPA) intensity activities based on Metabolic Equivalent Tasks (METs) derived from the Ainsworth's compendium of physical activity [15]. Physical activity levels are divided into the following categories: 0 minutes MVPA per week, 0 to 149 minutes MVPA per week, 150 to 299 minutes MVPA per week and 300 minutes MVPA per week and more. Physical inactivity is defined as less than 150 minutes per week MVPA [16].

Additionally, the questionnaire contained information on sitting behaviour, which is divided into sitting during transportation, working hours, watching television or using the computer at home. Participants are asked to fill in the number of hours and minutes on an average day in the past seven days during the week and on an average day during the weekend. This is similar to the sitting measure of the International Physical Activity Questionnaire (IPAQ) which has shown to be valid and reliable [17]. Sitting time was divided into the following 4 categories: (i) less than 4 hours a day, (ii) 4 to 8 hours a day, (iii) 8 to 11 hours a day and (iv) at least 11 hours a day or more [18]. Prolonged sitting time was defined as sitting at least for 8 hours a day or more.

Participants are physically inactive if they (i) are sitting on average more than 8 hours a day, irrespective of the physical activity, or (ii) are sitting on average 4 hours or more a day and are less active than 150 minutes MVPA per week.

Smoking

Participants are asked three questions to measure smoking behaviour: (i) whether they have smoked in the past month, and (ii) whether they have smoked in the past, for at least one year [19]. Smoking behaviour is categorized into non-smoker, past smoker and current smoker. Current smokers are defined as people who reported smoking in the past month. Past smokers reported smoking for at least one year, but did not smoke in the past month.

Loneliness

Loneliness is measured using De Jong Gierveld Loneliness Scale , which is a reliable and valid instrument to measure emotional, social and overall loneliness [20]. Possible answers on this 6-item scale are: (i) yes!, (ii) yes, (iii) more or less, (iv), no, (v) no!. The overall loneliness score is calculated by counting the neutral and negative (“no!”, “no”, or “more or less”) answers on items 4, 5 and 6 (social loneliness score) and by counting the positive (“more or less””, “yes” or “yes!”) answers on items 1,2 and 3 (emotional loneliness score). Subsequently, the overall loneliness score is categorized into: (i) not lonely (0-1), (ii) moderate lonely (2-4), (iii) severe lonely (5-6). Loneliness is defined as an overall loneliness score of 2 or higher [20].

Cardiovascular diseases

Participants are asked whether they have suffered or still suffer from one of the following cardiovascular diseases: angina pectoris, myocardial infarction, transient ischemic attack (TIA), stroke or peripheral arterial diseases (yes/no). Presence of a cardiovascular disease is defined as having at least one of the above mentioned diseases.

Hypertension

Hypertension is determined based on the blood pressure measurement in which the systolic and diastolic blood pressure is measured both three times consecutively. The average of the second and the third measurement is used to determine the presence of hypertension. Hypertension is present: (i) if the systolic blood pressure is higher than 140 mmHg or diastolic blood pressure is higher than 90 mmHg [21], or (ii) if participants indicate that they receive medication (i.e. diuretics, beta blockers, ACE-inhibitors, angiotensin 2 antagonists and calcium antagonists) for their hypertension .

High cholesterol

High cholesterol is defined based on direct laboratory measurements using the fasting blood samples and self-reported questionnaires. High cholesterol is present if (i) the Low Density Lipoprotein (LDL) is higher than 2.5 mmol/l or (ii) the ratio of total cholesterol (TC) and High Density Lipoprotein (HDL) is higher than 8 mmol/l [22] or (iii) participants indicate that they receive medication (i.e. simvastinin, atorvastatin, rosuvastatin, pravastatin, ezetimib) to lower their cholesterol levels.

Diabetes Mellitus

The presence of diabetes mellitus (or impaired blood glucose levels) is based on direct laboratory measurements using the fasting blood samples and self-reported questionnaires. Diabetes Mellitus is defined as: (i) glucose (fasting capillary blood) of 7.0 mmol/l or higher, or (ii) glucose (fasting capillary blood) lower than 7.0 mmol/l accompanied by HbA1C levels higher than 53 mmol/mol [23].

HbA1C provides additional information on the average blood glucose levels during the previous month, while glucose may differ during the day [23].

Obesity

Body weight and body height are measured during physical examination in order to determine their Body Mass Index (BMI=kg/m^2)[24]. Obesity is present if BMI is 30 kg/m^2 or higher [25].

Renal dysfunction

The presence of renal dysfunction is based on direct laboratory measurements (serum creatinine levels) using the fasting blood samples and self-reported questionnaires [26]. Subsequently, the estimated glomerular filtration rate (eGFR) is calculated using the 2009 CKD-EPI creatinine equation [27,28] in order to determine participant's renal function [28]. Renal dysfunction is present if (i) eGFR is lower than 60 ml/min/1.73 m^2 [29], or (ii) participants indicate that they receive medical treatment for the established renal dysfunction.

Depression

The level of depressive symptoms is measured using the Centre for Epidemiologic Studies Depression scale (CES-D). The CES-D consists of 20 items and is a reliable and valid tool to measure the current level of depressive symptoms in the general population [30]. Answer options for each item are: rarely or none of the time (0), some or a little of the time (1), occasionally or a moderate amount of time (2), and most of all of the time (3). Total score varying from 0 to 60, indicates the level of depressive symptoms, a higher score reflects a higher level of depressive symptoms. Depression is defined as (i) having a score of 16 or higher [31], or (ii) participants indicate that they receive medical treatment for their depressive symptoms.

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Supplementary file 2. Overview of assessment measures at baseline and follow up

Table 1. Assessment measures at baseline and follow up					
	Baseline	**3 months**	**6 months**	**9 months**	**12months**
GENERAL INFORMATION					
Age, gender, ethnicity, education and postal code	Q				
Participation in the Lifelines cohort	Q				
Medical family history	Q				
Health literacy (S-TOFHLA, 3-items)	Q				
RISK AND PROTECTIVE FACTORS					
Smoking	Q	Q	Q	Q	Q
Physical inactivity (SQUASH, IPAQ sitting measure)	Q	Q	Q	Q	Q
Mediterranean diet (FFQ)	Q	Q	Q	Q	Q
Alcohol consumption (FFQ)	Q	Q	Q	Q	Q
High cognitive activity (CRIq adapted)	Q	Q	Q	Q	Q
Loneliness (de Jong Gierveld, 6-items)	Q	Q	Q	Q	Q
Cardiovascular diseases (CVD)	Q	Q	Q	Q	Q
Obesity (body weight, height)	Q+ PE	Q	Q	Q	Q+PE
Hypertension (SBD, DBP)	Q+PE	Q	Q	Q	Q+PE
High cholesterol (LDL, HDL, TC)	Q+BS	Q	Q	Q	Q+BS
Diabetes Mellitus[1] (glucose,	Q+BS	Q	Q	Q	Q+BS

HbA1C)					
Renal dysfunction (eGFR)	Q+BS	Q	Q	Q	Q+BS
Depression (CES-D)	Q	Q	Q	Q	Q
OTHER PARAMETERS					
Medical treatment of disease	Q	Q	Q	Q	Q
Motivation to change lifestyle (MCLHB-DRR)	Q	Q	Q	Q	Q
Stages of change	Q	Q	Q	Q	Q
Hearing problems	Q	Q	Q	Q	Q
Subjective stress (LDI)	Q				Q
Memory complaints	Q				
Quality of life (2 items of SF36, VAS-score)	Q				Q
Perceived living environment	Q				Q
Compliance lifestyle advice per individual health behaviour		Q	Q	Q	Q
Compliance advice contact with GP		Q	Q	Q	Q

SQUASH Short Questionnaire to Assess Health-enhancing physical activity, *IPAQ* International Physical Activity Questionnaire, *FFQ* Food Frequency Questionnaire, *CRIq* Cognitive Reserve Index questionnaire, *CVD* Cardiovascular diseases, *SBP* Systolic Blood Pressure, *DBP* Diastolic Blood Pressure, *HDL* high-density lipoproteins, *LDL* low-density lipoproteins, *TC* total cholesterol, *HbA1C* Hemoglobin A1C, *eGFR* estimated Glomerular Filtration Rate, *CES-D* Centre for Epidemiological Studies Depression Scale, *MCLHB-DRR* Motivation to Change Lifestyle and Health Behavior for Dementia Risk Reduction Scale, LDI Long-term Difficulties Inventory, *SF36* Short Form 36 items, *VAS* Visual Analogue Scale

Q: Online questionnaire; PE: Physical examination; BS: Blood sample

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Beste Voornaam Achternaam,

Indien u wilt deelnemen aan dit onderzoek, vragen wij u dit toestemmingformulier door middel van een elektronische handtekening te ondertekenen. Hieronder vindt u de voorwaarde voor deelname aan dit onderzoek.

Wanneer u het toestemmingsformulier ondertekent verklaart u dat:

- u de informatiefolder met bijlagen en bovenstaande informatie heeft gelezen en hiermee voldoende bent geïnformeerd over het doel en de uitvoering van het onderzoek.
- U de mogelijkheid heeft gehad om aanvullende vragen te stellen (telefonisch of per mail), welke naar tevredenheid zijn beantwoord.
- u genoeg tijd had om te beslissen of u wilt deelnemen.
- u weet dat deelname vrijwillig is en dat u op ieder moment kan beslissen om toch niet mee te doen of te stoppen met het onderzoek.
- u weet dat u op de hoogte gesteld kan worden van medische relevante bevindingen.

U geeft toestemming:

– voor deelname aan het landelijk proef-bevolkingsonderzoek naar de beschermende en risicofactoren voor dementie (Demin studie).
– dat u in de toekomst opnieuw benaderd kan worden voor deelname aan aanvullend onderzoek.
– om uw onderzoeksgegevens te koppelen aan gegevens van het Centraal Bureau voor Statistiek (CBS), zoals uw gegevens over woonomgeving (bijvoorbeeld sportfaciliteiten).

Met vriendelijke groet,

Het Demin team
www.demin.nl

Ik verklaar dat ik deze proefpersoon volledig heb geïnformeerd over het genoemde onderzoek.

Als er tijdens het onderzoek informatie bekend wordt die de toestemming van de proefpersoon zou kunnen beïnvloeden, dan breng ik hem/haar daarvan tijdig op de hoogte.

Naam hoofdonderzoeker:
Handtekening: Datum:
Tijdstip:

De deelnemer krijgt een volledige informatiebrief, samen met een kopie van het getekende toestemmingsformulier.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	All pages, no results
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	21
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	21
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1

Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	23
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	23
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6
Objectives	#7	Specific objectives or hypotheses	7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7-8
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8-9
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-16
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or	n/a

		improving / worsening disease)	
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	10
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	16-20
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11, 16
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8-9
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8-9
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a, one recruitment strategy per

			memory clinic
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10-11
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	19
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	22

Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a, low risk
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	20-21
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16-17
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	22
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	22
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	21
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16, 22
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a, low risk
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	21

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	21
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	21
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	21
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

The uptake and effectiveness of a tailor-made online lifestyle program targeting modifiable risk factors for dementia among middle-aged descendants of people with recently diagnosed dementia: study protocol of a cluster randomised controlled trial (Demin study)

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The uptake and effectiveness of a tailor-made online lifestyle program targeting modifiable risk factors for dementia among middle-aged descendants of people with recently diagnosed dementia: study protocol of a cluster randomised controlled trial (Demin study)

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ABSTRACT

Introduction Descendants of dementia patients have a higher risk to develop dementia. This study aims to investigate the uptake and effectiveness of an online tailor-made lifestyle program for Dementia Risk Reduction (DRR) among middle-aged descendants of people with recently diagnosed late-onset dementia.

Methods and analysis Demin is a cluster randomised controlled trial, aiming to include 21 memory clinics of which thirteen will be randomly allocated to the passive (poster and flyer in waiting room) and eight to the active recruitment strategy (additional personal invitation by members of the team of the memory clinic). We aim to recruit 378 participants (40-60 years) with a parent who is recently diagnosed with Alzheimer's Disease or Vascular Dementia at one of the participating memory clinics. All participants receive a dementia risk assessment (online questionnaire, physical examination and blood sample) and subsequently an online tailor-made lifestyle advice regarding protective (Mediterranean diet, low/moderate alcohol consumption, high cognitive activity) and risk factors (physical inactivity, smoking, loneliness, cardiovascular disease, hypertension, high cholesterol, diabetes, obesity, renal dysfunction, depression) for dementia. The primary outcome is the difference in uptake between the two recruitment strategies. Secondary outcomes are change(s) in 1) the Lifestyle for Brain Health (LIBRA) score, 2) individual health behaviours, 3) health beliefs and attitudes towards DRR and 4) compliance to the tailor-made lifestyle advice. Outcomes will be measured at 3, 6, 9 and 12 months after baseline. The effectiveness of this online tailor-made lifestyle program will be evaluated by comparing Demin participants to a matched control group (Lifelines cohort).

Ethics and dissemination This study has been approved by the Dutch Ministry of Health, Welfare and Sport according to the Population Screening Act. All participants have to give online informed consent using SMS-tan. Findings will be disseminated through peer-reviewed journals and (inter)national conferences.

Trial registration number NTR7434

ARTICLE SUMMARY

Strengths and limitations of this study

- This is the first multicentre trial that focuses on dementia risk reduction in middle-aged descendants of recently diagnosed patients with Alzheimer's disease or Vascular dementia.
- The program gives participants insight in their risk and protective factors for dementia and provides a tailor-made online lifestyle advice with regard to thirteen modifiable risk factors for dementia, taking the stages of (health behaviour) change into account.
- The application ensures the privacy of the participants by using SMS-tan for logging in their personal account and signing the electronic informed consent form.
- The web-based application (demin.nl) functions fully automatically, making it easy to implement the study in other memory clinics and settings.
- Changing health behaviour is difficult and it is unclear whether a tailor-made online lifestyle advice is sufficient to change health behaviour and to maintain a healthy lifestyle.

KEY WORDS

Dementia

Health behaviour

Risk reduction behaviour

Lifestyle

Middle aged

INTRODUCTION

Dementia is considered a major public health concern [1]. Due to the ageing population the number of dementia cases will increase substantially in the next decades. In 2015, more than 46 million people worldwide were affected by dementia and this number is expected to increase to 131 million by 2050 [2]. This rise in people with dementia carries a high economic and social burden for society [1]. In 2015, global costs of dementia reached 818 billion US dollars and will increase further [3]. Currently, no curative treatments are available. Therefore, prevention is a key element to counteract the dementia epidemic [4,5].

The most common types of dementia are Alzheimer's disease (AD) (60-70%) ,Vascular dementia (VD) (15-20%) or a combination of AD and VD (mixed dementia) [6–8]. The presence of a first-degree relative with AD doubles the risk for developing AD [9]. This increased risk has several reasons. Firstly, descendants of people with AD more often have a higher genetic predisposition for AD (e.g. carrier of the Apo lipoprotein E (APOE) ε4 allele) [9]. Secondly, high blood pressure, vascular diseases and other vascular risk factors (i.e. diabetes type 2, obesity, hypercholesterolemia) often cluster in families [10]. Lastly, psychosocial behaviour runs in the family and also affects health behaviour and lifestyle [11,12]. Not surprisingly, individuals with a parent who is recently diagnosed with AD or VD often worry about their own risk of developing dementia. Therefore, this life event (parental diagnosis of dementia) might encourage the willingness of individuals to change their health behaviour [13].

Parental family history has been associated with an increased risk of dementia independently of known genetic risk factors [9,14]. Therefore, a healthy lifestyle might be beneficial for individuals with a positive family history, especially for APOE ε4 carriers [15–18]. Over the last decade, evidence of modifiable risk factors for dementia has been mounting [4,6,19]. The Lancet commission on dementia prevention, intervention and care demonstrated that 35% of the dementia cases is attributable to modifiable risk factors (i.e. less education, hearing loss, midlife hypertension, midlife obesity, smoking, depression, physical inactivity, social isolation and diabetes) and recommended to start

interventions including more childhood education, promotion of physical exercise, reduction of smoking, maintaining social engagement and management of hypertension, diabetes, obesity, depression and hearing loss [4,6,20]. Other major risk factors are hyperlipidaemia, coronary heart disease, renal dysfunction, Mediterranean diet and cognitive activity [19].

Only few studies examined the effectiveness of targeting these modifiable factors on cognitive decline and dementia incidence through a multi-domain intervention, such as the (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability) FINGER study [21], the (Prevention of Dementia by Intensive Vascular care) PreDIVA study [22] and the (The Multi-domain Alzheimer Preventive Trial) MAPT study [23]. These studies, with a follow-up varying from two to six years, found small or non-significant effects on cognition in older participants (e.g. >60 years) [21–23]. Starting multi-domain interventions earlier in life might be promising as cognitive decline begins already in midlife [24,25]. However, since dementia is mainly prevalent in the elderly, a long follow-up period of approximately 20 years would be required in order to determine the effectiveness of interventions on dementia incidence [24–26]. Furthermore, tailoring interventions improves the effectiveness of health behaviour change interventions [27]. Web-based interventions have the potential to support health behaviour change as there is the opportunity to tailor lifestyle advice [28–31]. They were especially effective when a theoretical basis or conceptual framework (e.g. Health belief model (HBM), Trans theoretical model (TTM), Theory of planned behaviour (TPB), I(integrated)-Change model [32–36]), behaviour change techniques (e.g. providing feedback on performance and information on the consequences of unhealthy behaviour) and several modes of delivery had been used [27].

The first challenge of health behaviour change interventions is to achieve a high level of uptake for screening (e.g. assessing risk and protective factors for dementia), reflecting the willingness to participate. A systematic review identified a large variation in uptake in health checks and lifestyle intervention programs [37], depending on the type of recruitment strategy. The two main types of strategies for recruitment are the active and passive recruitment strategy. Active recruitment involves a

personal invitation by the project staff and healthcare providers (e.g. proactive) and passive recruitment involves recruitment of participants through various channels such as flyers and advertisements (e.g. reactive) [38]. The most effective recruitment strategy is proactive referral from a healthcare provider, while displaying posters and flyers showed to be less effective [39,40]. Uptake also depends on other factors as described in social cognition models (e.g. knowledge, perceived susceptibility and severity, facilitators, benefits and barriers, and attitude towards such interventions) [32–36]. These factors are essential and useful to make a well-informed decision about dementia risk assessment, considering the possible benefits and harms. Therefore, information on dementia, the risk and protective factors for dementia, heritability, and how to tackle risk and protective factors for dementia are important factors in the development of a web-based intervention. A previous study showed that the majority of the Dutch general population is unaware of the relationship between modifiable risk factors and brain health, particularly regarding major cardiovascular risk factors (e.g. hypertension, hypercholesterolemia and coronary heart disease) [41]. It is shown that this lack of knowledge is a barrier to the uptake and maintenance of healthy behaviours for middle-aged individuals [42]. Having a parent who is recently diagnosed with AD or VD could have led to an increased knowledge on dementia and risk perception [13]. Therefore, middle-aged descendants of recently diagnosed people with AD or VD might be receptive to assess their risk and motivated to adopt a healthier lifestyle as they just realized their (familial) risk [13,43]. Although we expect that the uptake in the active recruitment strategy will be higher compared to the passive recruitment strategy, participants recruited via the passive recruitment strategy might be more intrinsically motivated to adopt and maintain their healthy lifestyle and less likely to drop out of the study.

To our knowledge, none of the health behaviour intervention studies were aimed at a specific group of middle-aged adults with increased risk for dementia due to their parental family history of dementia. Therefore, this study aims to investigate the uptake and effectiveness of a tailor-made online lifestyle program for dementia risk reduction among middle-aged descendants of recently diagnosed (in the last six months) people with AD or VD in the Netherlands. This will give insight in to what extent it is feasible to recruit middle-aged descendants of people with AD or VD at the memory clinics and

whether these potential participants are willing to participate in a tailor-made online lifestyle program in order to reduce their dementia risk.

METHODS AND ANALYSIS

Study setting and design

This study is a pragmatic cluster randomized controlled trial (RCT), including 21 participating memory clinics in the Netherlands who are randomly allocated to a passive or active recruitment of participants. Memory clinics allocated to the active recruitment strategy invite potential participants face-to-face by a member of the team of the memory clinic to participate in the tailor-made online lifestyle program for dementia risk reduction (also called the Demin study), next to posters and flyers that are placed in the waiting room of the memory clinic. Memory clinics allocated to the passive recruitment strategy, do not invite potential participants pro-actively, but invite potential participants to participate in the Demin study by posters and flyers that are placed in the waiting room of the memory clinic.

Patients with AD or VD (or their caregivers) receive an envelope either at the registration desk of the memory clinic or after the consult of the patient (only with active recruitment). This envelope is addressed to the middle-aged descendants of patients with recently diagnosed AD or VD and includes a patient information form (PIF) with information about the content of the study, the advantages and disadvantages of study participation and how potential participants can participate. Potential participants (one family member per patient) are asked to register themselves (e.g. making an account) on the Demin website (www.demin.nl), by using the memory clinic specific login access code, which is reported on the front page of the PIF and represents the memory clinic in which the parent was diagnosed. The decision to participate is confirmed by the participants by signing the online informed consent form (electronic signature by using SMS-tan). After signing this form, individuals from both recruitment strategies are able to log in to their personalized website 'My Demin' and continue the intervention in an equal manner. The personalized website 'My Demin' is secured and only accessible for the participant by logging in with their personal e-mail address, password and SMS-tan code. 'My Demin' contains the following information: 1) My personal (account) information, 2) Message inbox,

3) My online questionnaires, 4) My personal health profile including online tailor-made lifestyle advice. After participants have completed the online questionnaire, they automatically receive a message with a request to make an appointment for physical examination including a fasting blood sample. Moreover, participants can invite siblings to participate in the study in 'My Demin'. The functionalities provided by the Demin website are based on the literature and input we received from people with a parent with dementia (focus group discussions).

Randomization of memory clinics

To prevent contamination between the two recruitment strategies, randomization is performed at the level of the memory clinics. To enhance comparability between the intervention (participants of the active recruitment strategy) and control group (participants of the passive recruitment strategy), the memory clinics will be matched and randomised by a statistician, who is blind to the identity of the memory clinics and not involved in the study. Firstly, all participating memory clinics will be matched into pairs based on the following criteria: (i) number of newly diagnosed dementia (VD, AD or mixed dementia) patients seen per year (range vary from 60 to 350 patients per year) and (ii) the average social economic position (SEP) of the population living around the memory clinic (neighbourhood SEP), based on data from Statistics Netherlands [44]. Secondly, the matched memory clinics will be randomized (pairwise randomization) to an active recruitment strategy or passive recruitment strategy using a computer-generated random number list. As we expect a higher response rate in the active recruitment strategy group, we use an active : passive recruitment strategy ratio of 8:13 (see sample size calculations).

Study population

Eligible participants are middle-aged individuals (40-60 years old) with a parent who is recently (less than 6 months ago) diagnosed with AD or VD (or mixed dementia) at one of the participating memory clinics in the Netherlands (see acknowledgement). Individuals should provide informed consent, be able to fill out an online Dutch questionnaire. Pregnant women are excluded from participation.

Sample size calculations

The primary outcome measure is uptake, which is defined as the percentage of eligible individuals that signed the online informed consent form and completed baseline assessment (online questionnaire and physical examination and a fasting blood sample). In order to detect a difference of 20% in uptake between the passive and active recruitment strategy (30% versus 50%), we need 94 participants in each group to achieve a power of 80% with alpha levels of 0.05 (total = 188 participants). To take cluster randomization into account, we use the formula 1+ ((n-1)*ICC) (inflation factor), where n is the average number of included participants per memory clinic and the ICC the Intra Class Correlation [45]. The ICC is unknown, but an ICC of 0.05 is a common value for cluster randomized controlled trials in hospitals [46]. The estimated average of included participants per memory clinic per year is n=15 using a passive recruitment strategy and n=25 using an active recruitment strategy, taking into account non-response. With unequal cluster sizes, 'n' is replaced by 'm', where m is the sum of $(M)^2/sum(M)$ $((15^2+25^2) / (15+25))$ [47]. This results in a sample size inflation factor of (1+ ((21.25-1)*0.05)= 2.01. Therefore, the total number of participants needed is 378 (2.01 * 188). In order to recruit 378 participants, we need 21 memory clinics, of which eight memory clinics (responsible for 189 included participants) will be allocated to the active recruitment strategy and thirteen memory clinics (responsible for 189 included participants) will be allocated to the passive recruitment strategy.

Demin website

The Demin website is available for everyone and provides information about dementia, heredity of dementia, risk and protective factors for dementia, and how to tackle potential risk factors for dementia. The health information will be provided by written text and in an audio-visual format, such as a spoken animation, to assure inclusion of participants with different levels of health literacy [48]. According to the cognitive theory of multimedia learning (CTML), people process visual and auditory information through different channels [49,50]. It is known that health information provided by various channels, such as written text and spoken animations, improves information processing compared to information only provided through written text or spoken animations [49,50]. The

instructions for registration (making an account, signing informed consent) are also provided as written text as visual screenshots representing the steps of the registration process.

Online tailor-made lifestyle program for dementia risk reduction

After participants give online informed consent, participants have access to the online tailor-made lifestyle program for dementia risk reduction, which consists of 1) a dementia risk assessment and 2) an online tailor-made lifestyle advice including a personal health profile targeting risk and protective factors for dementia.

1. Dementia risk assessment

The dementia risk assessment consists of filling out an online questionnaire (in 'My Demin') and physical examination, including a fasting blood sample, at one of the 21 participating memory clinics in order to determine whether risk and protective factors are present. In order to minimize the amount of missing data, validation and skip-and-fail rules were implemented in the online questionnaire. Furthermore, automatic reminders are sent to the participant if the online questionnaire was not filled in within two weeks. Physical examination will be conducted by the team of the local memory clinic and includes the following measurements: height (in cm) (SECA 222 stadiometer), body weight (in kg) without shoes (SECA 761 scale), waist- and hip circumference (in cm) (SECA 200 measuring tape), and three measurements of diastolic and systolic blood pressure (in mmHg) (Welch Allyn 'Spot Vital Signs' [51]). After physical examination, which takes approximately 15 minutes, a fasting blood sample (maximum of 21 ml) is taken for direct laboratory measurement of glucose, HbA1C, total cholesterol, High-density-lipoprotein (HDL), Low-density-lipoprotein (LDL), triglycerides and serum creatinine. The results of the physical examination (height, body weight, blood pressure, waist- and hip circumference) are sent to the researcher (J. Vrijsen) to check the entry of the results by the participants. The results of the direct laboratory measurements are sent to the medical doctor (E.M. Abma) of the University Medical Centre Groningen to check for deviating values.

Risk and protective factors for dementia

Through the online questionnaire and physical examination, data on thirteen currently known protective (i.e. Mediterranean diet, low/moderate alcohol consumption, cognitive activity) and risk factors (i.e. physical inactivity, smoking, loneliness, cardiovascular diseases, hypertension, high cholesterol, diabetes mellitus, obesity, renal dysfunction, depression) for dementia are collected [6,19,52]. See **Table 1** for an overview of the assessment measures. The measurements of these risk and protective factors are described in **Supplementary file 1**.

Table 1. Assessment measures at baseline and follow up

	Baseline	**3 months**	**6 months**	**9 months**	**12months**
RISK AND PROTECTIVE FACTORS					
Smoking	Q	Q	Q	Q	Q
Physical inactivity (SQUASH, IPAQ)	Q	Q	Q	Q	Q
Mediterranean diet (FFQ)	Q	Q	Q	Q	Q
Alcohol consumption (FFQ)	Q	Q	Q	Q	Q
High cognitive activity (CRIq)	Q	Q	Q	Q	Q
Loneliness (de Jong Gierveld, 6-item)	Q	Q	Q	Q	Q
Cardiovascular diseases (CVD)	Q	Q	Q	Q	Q
Obesity (body weight, height)	Q+PE	Q	Q	Q	Q+PE
Hypertension (SBD, DBP)	Q+PE	Q	Q	Q	Q+PE
High cholesterol (LDL, HDL, TC)	Q+FBS	Q	Q	Q	Q+FBS
Diabetes Mellitus (glucose, HbA1C)	Q+FBS	Q	Q	Q	Q+FBS
Renal dysfunction (eGFR)	Q+FBS	Q	Q	Q	Q+FBS
Depression (CES-D)	Q	Q	Q	Q	Q

SQUASH Short Questionnaire to Assess Health-enhancing physical activity, *IPAQ* International Physical Activity Questionnaire, *FFQ* Food Frequency Questionnaire, *CRIq* Cognitive Reserve Index questionnaire (adapted), *CVD* Cardiovascular diseases, *SBP* Systolic Blood Pressure, *DBP* Diastolic Blood Pressure, *HDL*

high-density lipoproteins, *LDL* low-density lipoproteins, *TC* total cholesterol, *HbA1C* Haemoglobin A1C, *eGFR* estimated Glomerular Filtration Rate, *CES-D* Centre for Epidemiological Studies Depression Scale

Q: Online questionnaire, PE: Physical examination, FBS: Fasting blood sample

2a. Personal health profile

After completion of the baseline dementia risk assessment (including the data entry of the physical examination and laboratory measurements), a personal health profile is automatically provided in the personal account of the participants (My Demin). The personal health profile gives an overview of the presence of the risk and protective factors for dementia, without including the weight of the risk and protective factors. According to the Lifestyle for Brain Health (LIBRA) score, each risk and protective factor [19,52,53] is categorized into one of the following categories: 1) room for improvement, 2) remember to manage well, 3) keep this up (see **Table 2**). The "Keep this up" category represent factors that participants are currently managing well or diseases they do not have. The "Room for improvement" category represents the factors that could be improved by health behaviour change (e.g. quit smoking, become more physical active, change diet, drink less alcohol). The category "Remember to manage well" is assigned when a risk factor (i.e. cardiovascular disease, hypertension, high cholesterol, diabetes mellitus, renal dysfunction and depression) is present, but the disease is managed well as participants have regular meetings with their general practitioner for disease control (diabetes mellitus) or use medication for disease management (cardiovascular disease, hypertension, high cholesterol, renal dysfunction and depression) (see **Figure 1**).

[INSERT FIGURE 1 ABOUT HERE]

304 **Table 2.** Definition for the 3 categories in the personal health profile at baseline

Modifiable risk factors	Keep this up	Remember to manage well	Room for improvement
Diet	MIND-diet score = 14 points	n.a.	MIND-diet score < 14 points
Alcohol consumption	Average number of units of alcohol per week ≤ 7 and number of units per day is: ≤ 3 for women or ≤ 4 for men	n.a.	Average number of units of alcohol per week > 7 or number of units per day is: > 3 for women or > 4 for men
Cognitive activity	paid working hours ≥ 24 or CRIq score ≥ 50	n.a.	paid working hours < 24 and CRIq score < 50
Physical activity	(MVPA / week ≥ 150 and Sitting time ≤ 8 hours / day) or (MVPA / week < 150 and sitting time < 4 hours / day)	n.a.	(Sitting time > 8 hours / day) or (Sitting time ≥ 4 hours / day and MVPA / week < 150)
Smoking	Past or never smoker	n.a.	Current smoker
Loneliness	De Jong Gierveld score < 2	n.a.	De Jong Gierveld score ≥ 2
Cardiovascular diseases (CVD)	no CVD	at least one CVD and receives medical treatment	at least one CVD and no medical treatment
Weight	BMI ≥ 18.5 and BMI < 25.0	n.a.	BMI < 18.5 or BMI ≥ 25.0

Blood pressure	DBP < 90 mmHg and SBP < 140 and no medical treatment	DBP < 90 mmHg and SBP < 140 and medical treatment	DBP ≥ 90 mmHg or SBP ≥ 140 mmHg
Cholesterol	(LDL ≤ 2.5 mmol/l and TC/HDL ≤ 5) and no medical treatment	(LDL ≤ 2.5 mmol/l and TC/HDL ≤ 5) and medical treatment	LDL > 2.5 mmol/l or TC/HDL > 5
Diabetes Mellitus	glucose < 7.0 mmol and HbA1C ≤ 53 mmol/mol	(HbA1C ≤ 53 mmol/mol and medical treatment) or (glucose < 7.0 mmol and HbA1C > 53 mmol/mol and medical treatment)	(HbA1C > 53 mmol/mol and no medical treatment) or (glucose ≥ 7.0 mmol and HbA1C > 53 mmol/mol) or (glucose ≥ 7.0 mmol and HbA1C ≤ 53 mmol/mol and no medical treatment)
Kidney	eGFR ≥ 60 ml/min/1.73 m^2	eGFR < 60 ml/min/1.73 m^2 and medical treatment	eGFR < 60 ml/min/1.73 m^2 and no medical treatment
Depression	CES-D < 16 points	CES-D ≥ 16 points and medical treatment	CES-D ≥ 16 points and no medical treatment

MIND-diet Mediterranean-DASH Diet Intervention for Neurodegenerative Delay, *CRIq* Cognitive Reserve Index questionnaire, *MVPA* Moderate to vigorous physical activity, CVD Cardiovascular diseases, *BMI* Body mass index, *DBP* diastolic blood pressure, *SBP* systolic blood pressure, *LDL* low-

density lipoproteins, *TC* total cholesterol, *HDL* high-density lipoproteins, *HbA1C* Haemoglobin A1C, *eGFR* estimated Glomerular Filtration Rate, *CES-D* Centre for Epidemiological Studies Depression Scale

2b. Tailor-made online lifestyle advice for dementia risk reduction

Participants also receive an online tailor-made lifestyle advice targeting risk factors associated with dementia and following the Dutch guidelines for a healthy diet, alcohol consumption, physical activity, diabetes mellitus, renal dysfunction and cardiovascular health including cholesterol levels and BMI [54–58]. For each risk and protective factor, information is given about (i) the norm (cut-off point for not having this risk factor), (ii) the association between the risk factor and dementia and (iii) lifestyle advice how to tackle this factor. The online lifestyle advice was tailored to the participants based on (i) the presence of risk factors, (ii) the strength of the association between the risk factors and dementia [19,52] and (iii) the stages of change of the health behaviour related risk factors (physical inactivity, diet, alcohol consumption, smoking behaviour, cognitive activity, social activity). The stages of change are determined by asking "Which statement fits best for you?", where each answer option reflects one of the following stages of change: pre-contemplation, contemplation, preparation, action and maintenance [33]. It is known that participants who are in the preparation and action stage are more willing to change their health behaviour, therefore lifestyle advice for these factors are given first [33].

In case medically relevant findings are found, including untreated diabetes mellitus (glucose ≥ 7.0 mmol/l or (glucose ≥ 6.1 mmol/l and HbA1C > 53 mmol/mol)), untreated renal dysfunction (estimated Glomerular Filtration Rate (eGFR) ≤ 60 ml/min/1.73 m2) and increased risk for developing cardiovascular diseases (CVD) (CVD risk ≥ 10% according to the Dutch SCORE formula [58]), participants receive, in addition to the online tailor-made lifestyle advice, a separate message in their personal inbox with the recommendation to contact their general practitioner to verify the results and discuss whether treatment is needed.

Outcome measures and measurements

Participants are invited to fill in the online questionnaire at baseline and four times (3, 6, 9 and 12 months after baseline measurement) during one year follow-up. Physical examination, including the fasting blood sample for direct laboratory measurements, is only done at baseline and 12 months after

baseline measurement (see **Supplementary file 2**). Data from the online questionnaires and physical examination are stored automatically in an electronic Case Report Form (eCRF) data management program, which is only accessible by the researchers involved in this study. Data from the direct laboratory measurement are entered manually in the electronic Case Report Form (eCRF) data management program. Every month, memory clinics are requested to provide information about 1) the number of eligible participants (e.g. new cases of AD and VD), 2) the number of envelopes that are given away, and 3) any difficulties with the recruitment of participants. In order to keep participating memory clinics involved in the study, every three months newsletters are sent around and memory clinics are contacted monthly to evaluate the uptake.

Primary outcome

The primary outcome is the difference in uptake (e.g. the percentage of eligible people that signed the online informed consent form and completed risk assessment of the total number of eligible people) between the active and passive recruitment strategy. The total number of eligible people in each recruitment group (active versus passive) are based on the number of new cases of AD or VD in all memory clinics during the recruitment period, assuming an average of one child per dementia patient receiving the envelope with the PIF including a login access number. Due to privacy regulations it is not possible to collect data regarding the reasons for non-participation.

Secondary outcomes

Secondary outcomes include:

1) The change in Lifestyle for Brain Health (LIBRA) score. The LIBRA score has been validated among individuals in midlife and reflects an individual's potential to reduce their risk on developing late-onset dementia [52]. The LIBRA score consists of twelve currently known protective (i.e. Mediterranean diet, low/moderate alcohol consumption, cognitive activity) and risk factors (i.e. physical inactivity, smoking, cardiovascular diseases, hypertension, high cholesterol, diabetes mellitus, obesity, renal dysfunction, depression) for dementia (13, 14,31) and ranges from -5.9 (low risk for developing dementia) to 12.7 (high risk for developing dementia).

A one point increase in the LIBRA score is associated with a 19% higher risk for dementia [52,59]. The definitions and corresponding scores for the three protective and ten risk factors for dementia are described in **Table 3**.

Table 3. Definition of risk and protective factors for dementia in the LIBRA score and corresponding scores

Modifiable risk factors		**Definition**	**Score**
Protective factors			
1	High cognitive activity	Score ≥ 50 points on the Cognitive Reserve Index questionnaire (leisure time activities) (CRIq) or hours of paid work ≥ 24 hours	-3.2
2	Mediterranean diet	MIND-diet score (0-14) = 14 points	-1.7
3	Low/moderate alcohol consumption	Average number of glasses of alcohol a week ≤ 7 and number of glasses a day is: ≤ 3 glasses for women (no binge drinking) ≤ 4 glasses for men (no binge drinking)	-1.0
Risk factors			
4	Cardiovascular diseases (CVD)	Presence of at least one of the follow diseases: history of angina pectoris, myocardial infarction, transient ischemic attacks, stroke or peripheral arterial diseases	+1.0
5	Physical inactivity	Not fulfilling Dutch Norm for Physical activity defined as ≥ 150 min/week physical activity of moderate to vigorous intensity, measured with the SQUASH questionnaire	+1.1
6	Renal dysfunction	Estimated glomerular filtration rate ≤ 60 ml/min/1.73	+1.1
7	Diabetes Mellitus	Glucose (capillary blood) > 7.0 mmol/l or HbA1c > 53 mmol/mol	+1.3
8	High cholesterol	LDL > 2.5 mmol/l or TC/HDL > 5	+1.4
9	Smoking	Current smoker	+1.5

10	Obesity	BMI ≥ 30	+1.6
11	Hypertension	SBP > 140 mmHg or DBP > 90 mmHg	+1.6
12	Depression	Score ≥ 16 points on the Centre for Epidemiologic Studies Depression scale (CES-D)	+2.1

LDL low-density lipoproteins, *TC* total cholesterol, *HDL* high-density lipoproteins, *BMI* Body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

2) The change in the individual health behaviours, including physical activity (minutes of MVPA per week), diet (MIND-diet score; 0-14), alcohol consumption (number of glasses of alcohol per week), smoking behaviour (current smoker (yes/no) and number of cigarettes/cigars a day), cognitive activity (leisure-time cognitive activity score and number of hours paid work), loneliness (overall loneliness score; 0-6) and social activity (number of contacts per two weeks) and their stage of change over time. The stages of change are categorized into pre-contemplation (1), contemplation (2), preparation (3), action (4) and maintenance (5) [33].

3) Changes in beliefs and attitudes with regard to dementia risk reduction are measured using the Motivation to Change Lifestyle and Health Behaviour for Dementia Risk Reduction Scale (MCLHB-DRR scale) [60,61]. The MCLHB-DRR scale is based on the Health Belief Model [32], which explains health-related behaviours. Seven subscales of the Health Belief Model were included: perceived susceptibility, perceived severity, perceived benefits, perceives barriers, cues to action, general health motivation and self-efficacy. Participants are asked to rate all items on a 5-point Likert scale, ranging from strongly disagree (score=1) to strongly agree (score=5). A higher score on each subscale reflects a higher motivation to change their lifestyle and health behaviour for dementia risk reduction. The Dutch version of the MCLHB-DRR scale, consisting of 23 items, has shown to be valid in the Dutch general population aged between 30 and 80 years old [62].

4) Percentage of participants that indicated in the questionnaire that they have followed up the tailor-made online lifestyle advice ("On what risk factors did you receive lifestyle advice?" and "Did you

follow up the tailor-made lifestyle advice since the last questionnaire (with regard to [risk factor])"? , but also the percentage of participants that indicated that they have followed up the advice to consult their General Practitioner ("Did you have contact with your general practitioner after receiving feedback on the risk and protective factors?").

Statistical analyses

First, descriptive characteristics will be explored. The difference in uptake between the two recruitment strategies will be examined using multilevel logistic regression analyses in order to correct for clustering at memory clinic level. We will calculate the percentage with the corresponding 95% confidence interval (CI) and use an alpha of 0.05 to test statistical significance.

The effectiveness of the online tailor-made lifestyle program for dementia risk reduction will be determined by, firstly comparing the change in LIBRA score, the individual risk factors and the MCLHB-DRR score between the active and passive recruitment strategy, and secondly comparing participants of the Demin study (active and passive recruitment strategy) to a control group consisting of Lifelines participants (large population-based cohort study (n > 167.000)) (www.lifelines.nl)[63] in outcome. Lifelines participants (age 40 – 60 years) with a parent with dementia will be matched (using propensity scores) on non-modifiable risk factors (age, gender and education) for dementia to participants of the Demin. Subsequently, multilevel analyses will be performed to examine the change in the LIBRA score and the individual health behaviours over time. In addition, possible confounding and interaction effects will be identified and corrected for in the analysis (e.g. health literacy). We will calculate relative risks (RR) with 95% confidence intervals (CI) and use an alpha of 0.05 to test significance.

Adverse events

The risk classification of this intervention is considered negligible, since only information and health advice is provided. Serious adverse events as a result of the intervention are not expected, thus no data safety and monitoring board is installed. Potential participants are informed about possible adverse events. For example dementia risk assessment may help raising the awareness of their susceptibility in

order to motivate health behaviour change [32], however risk assessment could also have an unfavourable effect. Participants may become anxious about developing dementia and could experience more stress if they receive their health profile. Therefore, participants are clearly informed that the presence or absence of risk and protective factors is not a reassurance that they will develop dementia later in life. Furthermore, participants are informed that there is the possibility that unexpected medical findings can be found. In this case, participants receive a separate message in their personal inbox with the recommendation to contact their general practitioner to verify the results (hypertension, high cholesterol, renal dysfunction, diabetes) and discuss whether treatment is needed. Participants may consider online risk assessment as a privacy risk. In this study, all personal information is kept separately from the research data, and participants use a SMS-tan code to login in their personal account.

Patient and Public Involvement

Descendants of people with dementia were involved in the development of the Demin website. We assessed the knowledge, beliefs and attitudes towards dementia and dementia risk reduction among descendants of people with dementia (focus group discussions). The results of the focus group discussions were used to develop the Demin website in order to improve the participant recruitment and encourage health behaviour change among participants.

Ethics and dissemination

This study is approved by the Dutch ministry of Health, Welfare and Sport according to the Dutch Population Screening Act. Research which is considered to be Population Screening on the ground of the Population Screening Act, for which ministerial approval is required, does not have to be assessed on the basis of the Medical Research Involving Human Subjects Act [64]. Population screening is defined as 'medical research in persons carried out on an entire population or a category thereof aimed at the detection of certain types of disease or certain risk indicators for the benefit of the participating subjects'[65]. This project focuses on the attenuations of risk factors for dementia. Since these risk factors are merely lifestyle factors, a positive impact beyond dementia may be expected. Due to a

healthy lifestyle more healthy life years are added to people's lives, which may ultimately increase the risk on dementia as age is an important risk factor for dementia. This research is conducted in accordance to the international ethical guidelines [66].

All participants give informed consent to participate in this study, by signing an electronic informed consort form using SMS-tan (see **Supplementary file 3**). Authorship will be allocated using the guidelines for authorship defined by the International Committees of Medical Journal Editors (ICMJE) [67]. The results of the trial will be submitted to an international peer-reviewed journal and presented at national and international conferences.

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Author contributions JV contributed to the study concept and design, drafting of the manuscript and critical revision of the manuscript. NS and SR conceived the idea, were responsible for data acquisition, contributed to the study concept and design, and the critical revision of the manuscript. AAH, EM, PD, AW, FR, ROV, and EB contributed to the study concept and design, and the critical revision of the manuscript. All authors read and approved the final manuscript.

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Competing interests None declared

Data availability The data collected during this study will be available from the corresponding author upon reasonable request. This study aims to include data from 378 middle-aged participants recruited through participating memory clinics in the Netherlands. The final dataset will include data on physical examination, laboratory data from fasting blood samples and self-reported data including demographic characteristics, health and health behaviour. We will make the data and associated documentation available to users conditional on a data-sharing agreement that provides for: (1) a commitment to using the data only for research purposes, (2) a commitment to securing the data using appropriate computer technology, and (3) a commitment to destroying or returning the data after analyses are completed.

Patient consent Obligatory

Ethics approval This study is approved by the Dutch ministry of Health, Welfare and Sport according to the population screening act. In addition, all participating memory clinics approved the study.

Supplementary files

Supplementary file 1 Measures Dementia Risk Assessment

Supplementary file 2 Overview of measurements at baseline and follow up

Supplementary file 3 Consent form model

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Figure legends

Figure 1. An example of a personal health profile.

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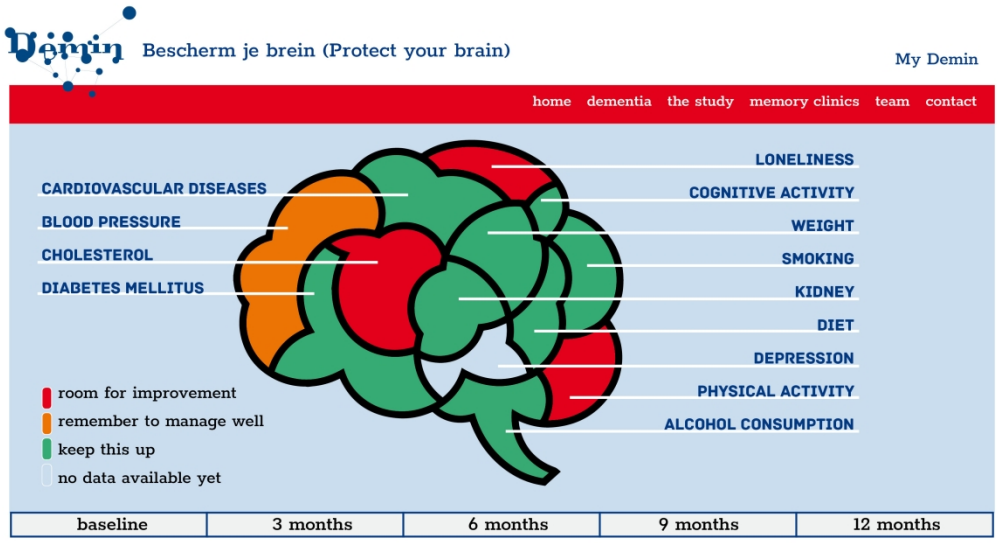

Figure 1. Example of a personal health profile

291x158mm (300 x 300 DPI)

Supplementary file 1: Measures Dementia Risk Assessment

Through the online questionnaire and physical examination, data on thirteen currently known protective (i.e. Mediterranean diet, low/moderate alcohol consumption, cognitive activity) and risk factors (i.e. physical inactivity, smoking, loneliness, cardiovascular diseases, hypertension, high cholesterol, diabetes mellitus, obesity, renal dysfunction, depression) for dementia are collected (6,14,41). The measurements of these risk and protective factors are described below.

Protective factors

Mediterranean diet

The Mediterranean-DASH diet intervention for neurodegenerative delay (MIND) has shown to slow down cognitive decline (1) and to decrease the risk of developing AD (2). Therefore, adherence to the MIND-diet is determined with a number of items of the Food Frequency Questionnaire (FFQ), which is a reliable and valid instrument to measure intake of a specified list of food items in the general populations (3,4). The following healthy food groups of the MIND-diet were included in the questionnaire, such as vegetables (especially green leafy vegetables), nuts, berries, beans, whole grains, seafood, poultry, olive oil (1,2). Also five unhealthy food groups of the MIND-diet including red meat, butter, cheese, sweets and fried/fast food were asked (1,2). Based on the intake of the food groups, adherence to the MIND-diet is determined (0-14). A score of 14 represent good adherence to the MIND-diet *(See **Table 1** for the MIND-diet scoring table).*

Table 1. MIND-diet scoring table (2)

MIND components	Recommended quantity	Max score
Whole grains	≥ 3 serving spoons / day	1
Green leafy	≥ 6 serving spoons / week	1
Other vegetables	≥ 1 serving spoon / day	1
Berries (including other fruits)	≥ 2 portions / week *	1
Red Meats and products	< 4 portions / week	1

Fish	≥ 1 portion / week	1
Poultry	≥ 2 portions / week	1
Beans	> 3 serving spoons /week	1
Nuts	≥ 5 portions /week *	1
Fast/ fried food	< 1time / week	1
Butter, margarine	< 1 teaspoon/ day	1
Cheese	< 1 slice / week	1
Pastries, sweets	< 5 portions / week	1
Olive Oil (used as primary oil)	yes	1
Total score		**14**

** One portion is a handful of the given component*

Low/moderate alcohol consumption

Alcohol consumption was measured using the FFQ (5), including questions regarding the frequency of alcohol use (e.g. no consumption last month, 1 day per month, 2-3 days per month, 1 day per week, 2-3 days per week, 4-5 days per week, 6-7 days per week) and the average number of glasses of alcohol per day (range from zero to more than twelve) was asked. Subsequently, the average number of glasses per month was calculated in order to classify participants into: (i) non-alcohol consumers, (ii) low/moderate alcohol consumers or (iii) excessive alcohol consumers (6). Participants adhere to the national recommendations for no to low/moderate alcohol consumption, if participants drink one glass or less alcohol per day on average, without binge drinking (more than three glasses alcohol on one day for females and more than four glasses alcohol on one day for males)) (7).

High cognitive activity

Cognitive activity is assessed with the leisure time section of the Cognitive Reserve Index questionnaire (CRIq) (22). CRIq aims to measure cognitive reserve (CR), which is based on education, working activity and leisure time activity. For this study we are interested in the current cognitive

activities of the participants. Therefore, cognitive activity is determined by measuring working activity and leisure time activity. The frequency of eighteen leisure time activity is asked (e.g. (i) never, (ii) less than once a month, (iii) once a month, (iv) once every 2 weeks, (v) several times a week). Subsequently, a leisure time cognitive activity score is calculated, ranging from to 18 to 108, where a score of 50 or higher represent high cognitive activity (based on results of a survey on the knowledge, beliefs and attitudes towards dementia risk reduction among the general population of Groningen, see Table 2 and 3).

Additionally, participants are asked if they have a paid job and if so how many hours they spend on their job per week. High cognitive activity is defined as (i) working at least 24 hours per week or (ii) a leisure time cognitive activity score of at least 50.

Table 2. Cognitive activity (leisure time) scores stratified for education level and having a paid job in a survey conducted among the general population in Groningen

Education level	**Work**	**Leisure time score**	
		mean(SD)	(min-max)
Low (n=105)	no work (n=75)	39.57 (11.16)	13 – 63
	work (n=30)	41.73 (11.12)	25 – 68
Middle (n=154)	no work (n=72)	47.03 (9.95)	26 – 76
	work (n=82)	45.20 (9.49)	25 – 64
High (n=390)	no work (n= 135)	51.93 (10.19)	18 – 75
	work (n=255)	48.32 (8.97)	23 – 74

Table 3. Cognitive activity (leisure time) scores stratified for education level and having a paid job in a survey conducted among the general population in Groningen (subgroup: 40 – 60 year old)

Education level	**Work**	**Leisure time score**	
		mean(SD)	(min-max)

Low (n=29)	no work (n=7)	39.71 (9.67)	21 – 49
	work (n=22)	40.50 (10.52)	25 – 58
Middle (n=68)	no work (n=9)	43. 89 (13.15)	26 – 66
	work (n=59)	46.34 (8.87)	25 – 64
High (n=140)	no work (n= 16)	50.56 (10.59)	37 – 69
	work (n=124)	49.91 (9.24)	23 – 74

Risk factors

Physical inactivity

Physical activity levels are determined using the Short Questionnaire to Asses Health enhancing physical activity (SQUASH), a self-reported questionnaire and commonly used instrument in the Netherlands to assess physical activity (8). The SQUASH questionnaire has shown to be valid and reliable in measuring physical activity among the Dutch population (9–12). The SQUASH questionnaire includes questions on multiple activities referring to an average week in the last month, including actively commuting (walking, cycling) to (voluntary) work or school, physical activity at (voluntary) work or school, household activities and leisure time activities, including walking, cycling, gardening and sports. Participants were asked to fill in how many days a week they engaged in the activities (frequency), the average time per day spent on each activity (hours and minutes; duration) and the intensity at which they did the activity (low, moderate, high) (8). A standardized methodology was followed to calculate physical activity levels. Briefly, results from the SQUASH questionnaire are automatically converted to minutes per week spent in light (LPA) and moderate to vigorous (MVPA) intensity activities based on Metabolic Equivalent Tasks (METs) derived from the Ainsworth's compendium of physical activity (13). Physical activity levels are divided into the following categories: 0 minutes MVPA per week, 0 to 149 minutes MVPA per week, 150 to 299 minutes MVPA per week and 300 minutes MVPA per week and more. Physical inactivity is defined as less than 150 minutes per week MVPA (14).

Additionally, the questionnaire contained information on sitting behaviour, which is divided into sitting during transportation, working hours, watching television or using the computer at home. Participants are asked to fill in the number of hours and minutes on an average day in the past seven days during the week and on an average day during the weekend. This is similar to the sitting measure of the International Physical Activity Questionnaire (IPAQ) which has shown to be valid and reliable (15). Sitting time was divided into the following 4 categories: (i) less than 4 hours a day, (ii) 4 to 8 hours a day, (iii) 8 to 11 hours a day and (iv) at least 11 hours a day or more (16). Prolonged sitting time was defined as sitting at least for 8 hours a day or more.

Participants are physically inactive if they (i) are sitting on average more than 8 hours a day, irrespective of the physical activity, or (ii) are sitting on average 4 hours or more a day and are less active than 150 minutes MVPA per week.

Smoking

Participants are asked three questions to measure smoking behaviour: (i) whether they have smoked in the past month, and (ii) whether they have smoked in the past, for at least one year (17). Smoking behaviour is categorized into non-smoker, past smoker and current smoker. Current smokers are defined as people who reported smoking in the past month. Past smokers reported smoking for at least one year, but did not smoke in the past month.

Loneliness

Loneliness is measured using De Jong Gierveld Loneliness Scale , which is a reliable and valid instrument to measure emotional, social and overall loneliness (18). Possible answers on this 6-item scale are: (i) yes!, (ii) yes, (iii) more or less, (iv), no, (v) no!. The overall loneliness score is calculated by counting the neutral and negative ("no!", "no", or "more or less") answers on items 4, 5 and 6 (social loneliness score) and by counting the positive ("more or less"", "yes" or "yes!") answers on items 1,2 and 3 (emotional loneliness score). Subsequently, the overall loneliness score is categorized into: (i) not lonely (0-1), (ii) moderate lonely (2-4), (iii) severe lonely (5-6). Loneliness is defined as an overall loneliness score of 2 or higher (18).

Cardiovascular diseases

Participants are asked whether they have suffered or still suffer from one of the following cardiovascular diseases: angina pectoris, myocardial infarction, transient ischemic attack (TIA), stroke or peripheral arterial diseases (yes/no). Presence of a cardiovascular disease is defined as having at least one of the above mentioned diseases.

Hypertension

Hypertension is determined based on the blood pressure measurement in which the systolic and diastolic blood pressure is measured both three times consecutively. The average of the second and the third measurement is used to determine the presence of hypertension. Hypertension is present: (i) if the systolic blood pressure is higher than 140 mmHg or diastolic blood pressure is higher than 90 mmHg (19), or (ii) if participants indicate that they receive medication (i.e. diuretics, beta blockers, ACE-inhibitors, angiotensin 2 antagonists and calcium antagonists) for their hypertension .

High cholesterol

High cholesterol is defined based on direct laboratory measurements using the fasting blood samples and self-reported questionnaires. High cholesterol is present if (i) the Low Density Lipoprotein (LDL) is higher than 2.5 mmol/l or (ii) the ratio of total cholesterol (TC) and High Density Lipoprotein (HDL) is higher than 5 mmol/l (19) or (iii) participants indicate that they receive medication (i.e. simvastinin, atorvastatin, rosuvastatin, pravastatin, ezetimib) to lower their cholesterol levels.

Diabetes Mellitus

The presence of diabetes mellitus (or impaired blood glucose levels) is based on direct laboratory measurements using the fasting blood samples and self-reported questionnaires. Diabetes Mellitus is defined as: (i) glucose (fasting capillary blood) of 7.0 mmol/l or higher, or (ii) glucose (fasting capillary blood) lower than 7.0 mmol/l accompanied by HbA1C levels higher than 53 mmol/mol (20).

HbA1C provides additional information on the average blood glucose levels during the previous month, while glucose may differ during the day (20).

Obesity

Body weight and body height are measured during physical examination in order to determine their Body Mass Index (BMI=kg/m^2)(21). Obesity is present if BMI is 30 kg/m^2 or higher (22).

Renal dysfunction

The presence of renal dysfunction is based on direct laboratory measurements (serum creatinine levels) using the fasting blood samples and self-reported questionnaires (23). Subsequently, the estimated glomerular filtration rate (eGFR) is calculated using the 2009 CKD-EPI creatinine equation (24,25) in order to determine participant's renal function (25). Renal dysfunction is present if (i) eGFR is lower than 60 ml/min/1.73 m^2 (26), or (ii) participants indicate that they receive medical treatment for the established renal dysfunction.

Depression

The level of depressive symptoms is measured using the Centre for Epidemiologic Studies Depression scale (CES-D). The CES-D consists of 20 items and is a reliable and valid tool to measure the current level of depressive symptoms in the general population (27). Answer options for each item are: rarely or none of the time (0), some or a little of the time (1), occasionally or a moderate amount of time (2), and most of all of the time (3). Total score varying from 0 to 60, indicates the level of depressive symptoms, a higher score reflects a higher level of depressive symptoms. Depression is defined as (i) having a score of 16 or higher (27), or (ii) participants indicate that they receive medical treatment for their depressive symptoms.

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Supplementary file 2. Overview of assessment measures at baseline and follow up

Table 1. Assessment measures at baseline and follow up					
	Baseline	**3 months**	**6 months**	**9 months**	**12months**
GENERAL INFORMATION					
Age, gender, ethnicity, education and postal code	Q				
Participation in the Lifelines cohort	Q				
Medical family history	Q				
Health literacy (S-TOFHLA, 3-items)	Q				
RISK AND PROTECTIVE FACTORS					
Smoking	Q	Q	Q	Q	Q
Physical inactivity (SQUASH, IPAQ sitting measure)	Q	Q	Q	Q	Q
Mediterranean diet (FFQ)	Q	Q	Q	Q	Q
Alcohol consumption (FFQ)	Q	Q	Q	Q	Q
High cognitive activity (CRIq adapted)	Q	Q	Q	Q	Q
Loneliness (de Jong Gierveld, 6-items)	Q	Q	Q	Q	Q
Cardiovascular diseases (CVD)	Q	Q	Q	Q	Q
Obesity (body weight, height)	Q+ PE	Q	Q	Q	Q+PE
Hypertension (SBD, DBP)	Q+PE	Q	Q	Q	Q+PE
High cholesterol (LDL, HDL, TC)	Q+BS	Q	Q	Q	Q+BS
Diabetes Mellitus[1] (glucose,	Q+BS	Q	Q	Q	Q+BS

HbA1C)					
Renal dysfunction (eGFR)	Q+BS	Q	Q	Q	Q+BS
Depression (CES-D)	Q	Q	Q	Q	Q
OTHER PARAMETERS					
Medical treatment of disease	Q	Q	Q	Q	Q
Motivation to change lifestyle (MCLHB-DRR)	Q	Q	Q	Q	Q
Stages of change	Q	Q	Q	Q	Q
Hearing problems	Q	Q	Q	Q	Q
Subjective stress (LDI)	Q				Q
Memory complaints	Q				
Quality of life (2 items of SF36, VAS-score)	Q				Q
Perceived living environment	Q				Q
Compliance lifestyle advice per individual health behaviour		Q	Q	Q	Q
Compliance advice contact with GP		Q	Q	Q	Q

SQUASH Short Questionnaire to Assess Health-enhancing physical activity, *IPAQ* International Physical Activity Questionnaire, *FFQ* Food Frequency Questionnaire, *CRIq* Cognitive Reserve Index questionnaire, *CVD* Cardiovascular diseases, *SBP* Systolic Blood Pressure, *DBP* Diastolic Blood Pressure, *HDL* high-density lipoproteins, *LDL* low-density lipoproteins, *TC* total cholesterol, *HbA1C* Hemoglobin A1C, *eGFR* estimated Glomerular Filtration Rate, *CES-D* Centre for Epidemiological Studies Depression Scale, *MCLHB-DRR* Motivation to Change Lifestyle and Health Behavior for Dementia Risk Reduction Scale, LDI Long-term Difficulties Inventory, *SF36* Short Form 36 items, *VAS* Visual Analogue Scale

Q: Online questionnaire; PE: Physical examination; BS: Blood sample

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Aangemeld op: 01-02-2020 10:01:16

01-02-2020 10:06:24

Beste Voornaam Achternaam,

Indien u wilt deelnemen aan dit onderzoek, vragen wij u dit toestemmingformulier door middel van een elektronische handtekening te ondertekenen. Hieronder vindt u de voorwaarde voor deelname aan dit onderzoek.

Wanneer u het toestemmingsformulier ondertekent verklaart u dat:

- u de informatiefolder met bijlagen en bovenstaande informatie heeft gelezen en hiermee voldoende bent geïnformeerd over het doel en de uitvoering van het onderzoek.
- U de mogelijkheid heeft gehad om aanvullende vragen te stellen (telefonisch of per mail), welke naar tevredenheid zijn beantwoord.
- u genoeg tijd had om te beslissen of u wilt deelnemen.
- u weet dat deelname vrijwillig is en dat u op ieder moment kan beslissen om toch niet mee te doen of te stoppen met het onderzoek.
- u weet dat u op de hoogte gesteld kan worden van medische relevante bevindingen.

U geeft toestemming:

– voor deelname aan het landelijk proef-bevolkingsonderzoek naar de beschermende en risicofactoren voor dementie (Demin studie).
– dat u in de toekomst opnieuw benaderd kan worden voor deelname aan aanvullend onderzoek.
– om uw onderzoeksgegevens te koppelen aan gegevens van het Centraal Bureau voor Statistiek (CBS), zoals uw gegevens over woonomgeving (bijvoorbeeld sportfaciliteiten).

Met vriendelijke groet,

Het Demin team
www.demin.nl

Ik verklaar dat ik deze proefpersoon volledig heb geïnformeerd over het genoemde onderzoek.

Als er tijdens het onderzoek informatie bekend wordt die de toestemming van de proefpersoon zou kunnen beïnvloeden, dan breng ik hem/haar daarvan tijdig op de hoogte.

Naam hoofdonderzoeker:
Handtekening: Datum:
Tijdstip:

De deelnemer krijgt een volledige informatiebrief, samen met een kopie van het getekende toestemmingsformulier.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	All pages, no results
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	21
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	21
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1

Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	23
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	23
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6
Objectives	#7	Specific objectives or hypotheses	7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7-8
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8-9
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-16
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or	n/a

		improving / worsening disease)	
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	10
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	16-20
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11, 16
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8-9
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8-9
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a, one recruitment strategy per

			memory clinic
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10-11
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	19
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	22

Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a, low risk
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	20-21
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16-17
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	22
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	22
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	21
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	16, 22
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a, low risk
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	21

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	21
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	21
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	21
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a