Towards dementia risk reduction among individuals with a parental family history of dementia

Vrijsen, Joyce

DOI:
10.33612/diss.170947423

CHAPTER 7

UPTAKE AND EFFECTIVENESS OF A TAILOR-MADE ONLINE LIFESTYLE PROGRAMME 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)

Joyce Vrijsen, Ameen Abu-Hanna, Els L.M. Maeckelberghe, Peter Paul De Deyn,
Andrea F. de Winter, Fransje E. Reesink, Richard C. Oude Voshaar,
Erik Buskens, Sophia E. de Rooij, Nynke Smidt
on behalf of the Demin consortium.

BMJ Open 2020; 10:e039439

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 programme 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 programme 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.

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) **ε**4 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 **ε**4 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 programmes (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 programme 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 programme in order to reduce their dementia risk.

METHODS AND ANALYSIS

Study setting and design

This study is a pragmatic cluster randomised 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 programme 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 randomised (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 randomised 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 programme for dementia risk reduction

After participants give online informed consent, participants have access to the online tailor-made lifestyle programme 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.

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	12 months
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

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**).

Figure 1. An example of a personal health profile.

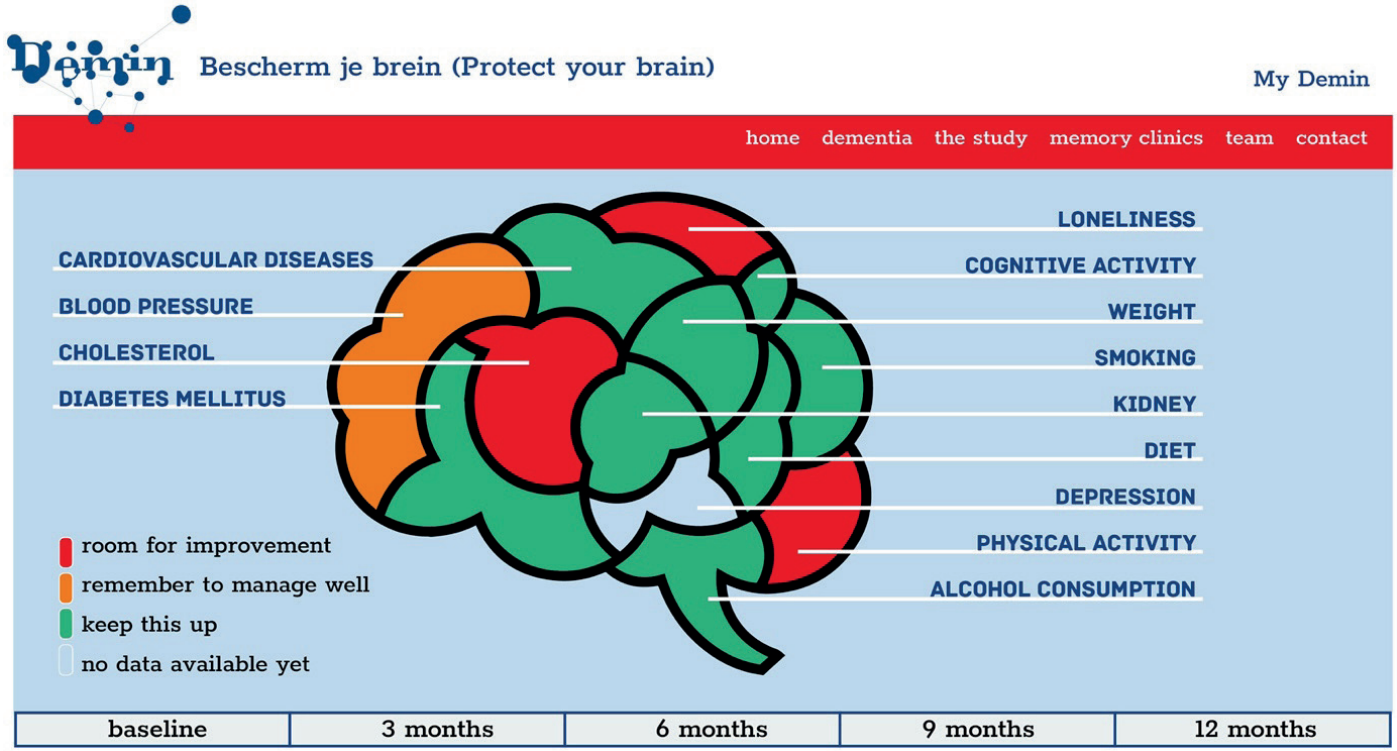

Table 2. Definition for the 3 categories in the personal health profile at baseline

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 mmHg and no medical treatment	DBP < 90 mmHg and SBP < 140 mmHg 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

Modifiable risk factors	Keep this up	Remember to manage well	Room for improvement
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

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 (59)), 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 programme, 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 programme. 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 (52,60). 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) (61,62). 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 (63).

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 programme 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)(64) 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 (65). 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'(66). 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 (67).

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) (68). The results of the trial will be submitted to an international peer-reviewed journal and presented at national and international conferences.

Acknowledgements

The authors would like to thank the developers of the Demin website (Bruna&Bruna, Rocket Industries, Centric and Research Data Support from the University Medical Centre Groningen) to make this research possible and the Board of Directors and the collaborators of the participating memory clinics for the local approval and collaboration to conduct this multicentre study: Albert Schweitzer hospital (Dordrecht), Gelre hospital (Apeldoorn), University Medical Centre Groningen (Groningen), Medical Centre Leeuwarden (Leeuwarden), Nij Smellinghe (Drachten), Isala Zwolle (Zwolle), Martini hospital (Groningen), Haga hospital (Den Haag), Scheper hospital (Emmen), Refaja hospital (Stadskanaal), St. Jans Gasthuis (Weert), University Medical

Centre Utrecht (Utrecht), Reinier de Graaf Gasthuis (Delft), Maxima Medical Centre (Eindhoven), Radboud University Medical Centre (Nijmegen), TweeSteden hospital (Tilburg), Erasmus Medical Centre (Rotterdam), Ommelanden Hospital Groningen (Scheemda), Rijnstate hospital (Arnhem and Zevenaar).

Collaborators

The members of the Demin consortium are: Elske Marije Abma (MD), Ameen Abu-Hanna (PhD), Erik Buskens (MD, PhD), Jürgen Claassen (MD, PhD), Peter Paul De Deyn (MD, PhD), Theo Feitsma (MD), Liesbeth Hempenius (MD, PhD), Jan Hoogmoed (MD), Ad Kamper (MD, PhD), Dineke Koek (MD, PhD), Jolijn Kragt (MD, PhD), Joep Lagro (MD, PhD), Els Lambooij (MD), Marc Langedijk (MD), Els Maeckelberghe (PhD), Francesco Mattace Raso (MD, PhD), Marieke Meinardi (MD, PhD), Richard Oude Voshaar (MD, PhD), Fransje Reesink (MD, PhD), Sophia de Rooij (MD, PhD), Antoinette Scheepmaker (MD), Nynke Smidt (PhD), Petra Spies (MD), Diana Taekema (MD, PhD), Jos Verkuyl (MD), Ralf Vingerhoets (MD), Joyce Vrijsen (MSc), Andrea de Winter (PhD).

REFERENCES

1. World Health Organization (WHO). Dementia: A public health priority. 2012.
2. Prince M, Wimo A, Guerchet M, Gemma-Claire A, Wu Y-T, Prina M. World Alzheimer Report 2015: the global impact of dementia - an analysis of prevalence, incidence, cost and trends. Alzheimer's Dis Int. 2015;84.
3. Wimo A, Guerchet M, Ali G-C, Wu Y-T, Prina AM, Winblad B, et al. The worldwide costs of dementia 2015 and comparisons with 2010. Alzheimer's Dement. 2017;13(1):1–7.
4. Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C, Ministers GH and S, et al. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. Lancet Neurol. 2014 Aug;13(8):788–94.
5. Sindi S, Mangialasche F, Kivipelto M. Advances in the prevention of Alzheimer's Disease. F1000Prime Rep. 2015;7:50.
6. Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, et al. The Lancet Commissions Dementia prevention, intervention, and care. Lancet. 2017;390(10113):2673–734.
7. Fratiglioni L, Launer LJ, Andersen K, Breteler MMB, Copeland JRM, Dartigues JF, et al. Incidence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurology. 2000;54(11 SUPPL. 5):1–10.
8. Rizzi L, Rosset I, Roriz-Cruz M. Global epidemiology of dementia: Alzheimer's and vascular Types. Biomed Res Int. 2014;2014:1–8.
9. Scarabino D, Gambina G, Broggio E, Pelliccia F, Corbo RM. Influence of family history of dementia in the development and progression of late-onset Alzheimer's disease. Am J Med Genet Part B Neuropsychiatr Genet. 2016 Mar;171(2):250–6.
10. van Exel E, Eikelenboom P, Comijs H, Frölich M, Smit JH, Stek ML, et al. Vascular factors and markers of inflammation in offspring with a parental history of late-onset Alzheimer disease. Arch Gen Psychiatry. 2009 Nov 1;66(11):1263–70.
11. Muñoz M, Pong-Wong R, Canela-Xandri O, Rawlik K, Haley CS, Tenesa A. Evaluating the contribution of genetics and familial shared environment to common disease using the UK Biobank. Nat Genet. 2016 Jul 18;48(9):980–3.
12. Borenstein AR, Copenhaver CI, Mortimer JA. Early-Life Risk Factors for Alzheimer Disease. Alzheimer Dis Assoc Disord. 2006 Jan;20(1):63–72.
13. Andersson L, Stanich J. Life events and their impact on health attitudes and health behavior. Arch Gerontol Geriatr. 1996 Sep;23(2):163–77.
14. Wolters FJ, van der Lee SJ, Koudstaal PJ, van Duijn CM, Hofman A, Ikram MK, et al. Parental family history of dementia in relation to subclinical brain disease and dementia risk. Neurology. 2017 Apr 25;88(17):1642–9.
15. Licher S, Ahmad S, Karamujić-Čomić H, Voortman T, Leening MJG, Ikram MA, et al. Genetic predisposition, modifiable-risk-factor profile and long-term dementia risk in the general population. Nat Med. 2019 Sep 26;25(9):1364–9.
16. Lourida I, Hannon E, Littlejohns TJ, Langa KM, Hyppönen E, Kuzma E, et al. Association of lifestyle and genetic risk with incidence of dementia. JAMA. 2019 Aug 6;322(5):430.
17. Dekhtyar S, Marseglia A, Xu W, Darin-Mattsson A, Wang HX, Fratiglioni L. Genetic risk of dementia mitigated by cognitive reserve: A cohort study. Ann Neurol. 2019 Jul 1;86(1):68–78.

18. Kivipelto M, Rovio S, Ngandu T, Kåreholt I, Eskelinen M, Winblad B, et al. Apolipoprotein E epsilon4 magnifies lifestyle risks for dementia: a population-based study. J Cell Mol Med. 2008 Dec;12(6B):2762–71.
19. Deckers K, van Boxtel MPJ, Schiepers OJG, de Vugt M, Muñoz Sánchez JL, Anstey KJ, et al. Target risk factors for dementia prevention: a systematic review and Delphi consensus study on the evidence from observational studies. Int J Geriatr Psychiatry. 2015 Mar;30(3):234–46.
20. de Bruijn RF, Bos MJ, Portegies ML, Hofman A, Franco OH, Koudstaal PJ, et al. The potential for prevention of dementia across two decades: the prospective, population-based Rotterdam Study. BMC Med. 2015 Dec 21;13(1):132.
21. Ngandu T, Lehtisalo J, Solomon A, Levälahti E, Ahtiluoto S, Antikainen R, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. Lancet. 2015 Jun;385(9984):2255–63.
22. van Charante EPM, Richard E, Eurelings LS, van Dalen J-W, Ligthart SA, van Bussel EF, et al. Effectiveness of a 6-year multidomain vascular care intervention to prevent dementia (preDIVA): a cluster-randomised controlled trial. Lancet. 2016;388(10046):797–805.
23. Vellas B, Carrie I, Gillette-Guyonnet S, Touchon J, Dantoine T, Dartigues JF, et al. MAPT Study: A Multidomain Approach for Preventing Alzheimer's Disease: Design and Baseline Data. J Prev Alzheimer's Dis. 2014;1(1):13–22.
24. Singh-Manoux A, Kivimaki M, Glymour MM, Elbaz A, Berr C, Ebmeier KP, et al. Timing of onset of cognitive decline: results from Whitehall II prospective cohort study. BMJ. 2012 Jan 5;344:d7622.
25. Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011 May;7(3):280–92.
26. Rajan KB, Wilson RS, Weuve J, Barnes LL, Evans DA. Cognitive impairment 18 years before clinical diagnosis of Alzheimer disease dementia. Neurology. 2015 Sep 8;85(10):898–904.
27. Webb TL, Joseph J, Yardley L, Michie S. Using the internet to promote health behavior change: a systematic review and meta-analysis of the impact of theoretical basis, use of behavior change techniques, and mode of delivery on efficacy. J Med Internet Res. 2010 Jan 17;12(1):e4.
28. van Stralen MM, de Vries H, Mudde AN, Bolman C, Lechner L. The long-term efficacy of two computer-tailored physical activity interventions for older adults: main effects and mediators. Health Psychol. 2011 Jul;30(4):442–52.
29. Schulz DN, Kremers SPJ, Vandelanotte C, van Adrichem MJG, Schneider F, Candel MJJM, et al. Effects of a web-based tailored multiple-lifestyle intervention for adults: a two-year randomised controlled trial comparing sequential and simultaneous delivery modes. J Med Internet Res. 2014 Jan 27;16(1):e26.
30. Jahangiry L, Montazeri A, Najafi M, Yaseri M, Farhangi MA. An interactive web-based intervention on nutritional status, physical activity and health-related quality of life in patient with metabolic syndrome: a randomised-controlled trial (The Red Ruby Study). Nutr Diabetes. 2017 Jan 9;7(1):e240.

31. Murray E. Web-based interventions for behavior change and self-management: potential, pitfalls, and progress. Med 20. 2012;1(2):e3.
32. Janz NK, Becker MH. The Health Belief Model: A Decade Later. Heal Educ Behav. 1984 Jan 1;11(1):1–47.
33. Prochaska JO, Velicer WF. The transtheoretical model of health behavior change. Am J Health Promot. 1997;12(1):38–48.
34. Hagger MS, Chatzisarantis NLD. Integrating the theory of planned behaviour and self-determination theory in health behaviour: A meta-analysis. Br J Health Psychol. 2009 May;14(2):275–302.
35. Bandura A. Self-efficacy conception of anxiety. Anxiety Res. 1988;1(2):77–98.
36. de Vries H. An Integrated Approach for Understanding Health Behavior; The I-Change Model as an Example. Psychol Behav Sci Int J. 2017;2(2).
37. Koopmans B, Nielen MM, Schellevis FG, Korevaar JC. Non-participation in population-based disease prevention programmes in general practice. BMC Public Health. 2012 Dec 9;12(1):856.
38. Yancey AK, Ortega AN, Kumanyika SK. Effective recruitment and retention of minority research particioants. Annu Rev Public Health. 2006 Apr 13;27(1):1–28.
39. Bracken K, Askie L, Keech AC, Hague W, Wittert G. Recruitment strategies in randomised controlled trials of men aged 50 years and older: a systematic review. BMJ Open. 2019;9(4).
40. Van Der Meer V, Nielen MM, Drenthen AJ, Vliet M Van, Assendelft WJ, Schellevis FG. Cardiometabolic prevention consultation in the Netherlands: screening uptake and detection of cardiometabolic risk factors and diseases – a pilot study. BMC Fam Pract. 2013;14(1):1.
41. Heger I, Deckers K, van Boxtel M, de Vugt M, Hajema K, Verhey F, et al. Dementia awareness and risk perception in middle-aged and older individuals: baseline results of the MijnBreincoach survey on the association between lifestyle and brain health. BMC Public Health. 2019 Dec 3;19(1):678.
42. Kelly S, Martin S, Kuhn I, Cowan A, Brayne C, Lafortune L. Barriers and facilitators to the uptake and maintenance of healthy behaviours by people at mid-life: A rapid systematic review. Vol. 11, PLoS ONE. Public Library of Science; 2016.
43. Rosenberg A, Coley N, Soulier A, Kulmala J, Soininen H, Andrieu S, et al. Experiences of dementia and attitude towards prevention: a qualitative study among older adults participating in a prevention trial. BMC Geriatr. 2020 Dec 12;20(1):99.
44. Centraal Bureau voor de Statistiek. Percentage hoger opgeleiden van 15 laar en ouder - Bevolkingskern (2011) [Internet]. 2011 [cited 2019 Feb 18]. Available from: http://www.cbsinuwbuurt.nl/#bevolkingskern2011_percentage_inwoners_hogere_opleiding
45. Donner A, Birkett Ni, Buck C. Randomization by cluster. Am J Epidemiol. 1981 Dec 1;114(6):906–14.
46. Kul S, Vanhaecht K, Panella M. Intraclass correlation coefficients for cluster randomised trials in care pathways and usual care: hospital treatment for heart failure. BMC Health Serv Res. 2014 Dec 24;14(1):84.
47. Rutterford C, Copas A, Eldridge S. Methods for sample size determination in cluster randomised trials. Int J Epidemiol. 2015 Jun;44(3):1051–67.

48. Meppelink CS, Weert JC van, Haven CJ, Smit EG. The Effectiveness of Health Animations in Audiences With Different Health Literacy Levels: An Experimental Study. J Med Internet Res. 2015;17(1).
49. Mayer R. Multimedia Learning. In: Ross BH, editor. The psychology of learning and motivation. San Diego: Academic Press; 2002. p. 85–139.
50. Paivio A. Mental representations : a dual coding approach. Oxford University Press; 1986.
51. Jones CR, Taylor K, Poston L, Shennan AH. Validation of the Welch Allyn "Vital Signs" oscillometric blood pressure monitor. J Hum Hypertens. 2001 Mar;15(3):191–5.
52. Schiepers OJG, Köhler S, Deckers K, Irving K, O'Donnell CA, van den Akker M, et al. Lifestyle for Brain Health (LIBRA): a new model for dementia prevention. Int J Geriatr Psychiatry. 2018 Feb;33:167–75.
53. Vos SJB, van Boxtel MPJ, Schiepers OJG, Deckers K, de Vugt M, Carri?re I, et al. Modifiable Risk Factors for Prevention of Dementia in Midlife, Late Life and the Oldest-Old: Validation of the LIBRA Index. J Alzheimer's Dis. 2017 May 11;58(2):537–47.
54. De Grauw W, De Leest K, Schenk P, Scherpbier-De Haan N, Tjin-A-Ton J, Tuut M, et al. NHG-Standaard Chronische Nierschade. TPO - Prakt. 2018;13(5):26–9.
55. Kromhout D, Spaaij CJK, De Goede J, Weggemans RM, Brug J, Geleijnse JM, et al. The 2015 Dutch food-based dietary guidelines. Eur J Clin Nutr. 2016 Aug 1;70(8):869–78.
56. Weggemans RM, Backx FJG, Borghouts L, Chinapaw M, Hopman MTE, Koster A, et al. The 2017 Dutch Physical Activity Guidelines. Int J Behav Nutr Phys Act. 2018 Jun 25;15(1):58.
57. Rutten G, De Grauw W, Nijpels G, Houweling S, Van de Laar F, Bilo H, et al. NHG-Standaard Diabetes mellitus type 2. 2013.
58. Tjin-A-Ton J, Konings K, Wiersma T. Nieuwe NHG-Standaard CVRM: schatten, overwegen en maatwerk. Huisarts Wet. 2019;62(4):55–7.
59. van Dis SJ, Kromhout D, Geleijnse JM, Boer JMA, Verschuren WMM. Evaluation of cardiovascular risk predicted by different score equations: the Netherlands as an example. Eur J Cardiovasc Prev Rehabil. 2010;17:244–9.
60. Deckers K, Köhler S, van Boxtel M, Verhey F, Brayne C, Fleming J, et al. Lack of associations between modifiable risk factors and dementia in the very old: findings from the Cambridge City over-75s cohort study. Aging Ment Health. 2017 Feb 2;1–7.
61. Kim S, Sargent-Cox K, Cherbuin N, Anstey KJ. Development of the motivation to change lifestyle and health behaviours for dementia risk reduction scale. Dement Geriatr Cogn Dis Extra. 2014 May 5;4(2):172–83.
62. Beaton DE, Bombardier C, Guillemin F, Ferraz MB. Guidelines for the process of cross-cultural adaptation of self-report measures. Spine. 2000;25(24):3186–91.
63. Joxhorst T, Vrijsen J, Niebuur J, Smidt N. Cross-cultural validation of the motivation to change lifestyle and health behaviours for dementia risk reduction scale in the Dutch general population. BMC Public Health. 2020 Jul 20;20(1):788.
64. Scholtens S, Smidt N, Swertz MA, Bakker SJL, Dotinga A, Vonk JM, et al. Cohort Profile: LifeLines, a three-generation cohort study and biobank. Int J Epidemiol. 2015 Aug;44(4):1172–80.
65. Central Committee on Research Involving Human Subjects. Population Screening Act [Internet]. 2020. Available from: https://english.ccmo.nl/investigators/legal-framework-for-medical-scientific-research/laws/population-screening-act

66. Central Committee on Research Involving Human Subjects. The definition of population screening [Internet]. 2020. Available from: https://english.ccmo.nl/investigators/types-of-research/other-types-of-research/population-research/definition
67. Council for International Organizations of Medical Sciences. International ethical guidelines for biomedical research involving human subjects. Bull Med Ethics. 2002;182(Oct):17–23.
68. The International Committee of Medical Journal Editors. Recommendations for the conduct, reporting, editing and publication of scholarly work in medical journals. 2019.