Prevention of cognitive decline

Effectiveness of physical exercise and vitamin B supplementation

Jannique van Uffelen

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Promotor: prof. W. van Mechelen
Copromotoren: dr. M.J.M Chin A Paw and dr. M. Hopman-Rock

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promotor:	prof.dr. W. van Mechelen
copromotoren:	dr. M.J.M. Chin A Paw
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Levensloop

Achterin vindt u mijn officiële curriculum vitae
met opleidingen en diploma's die ik heb behaald
met dit proefschrift wordt daar weer iets aan toegevoegd
doordat de 's' van mijn 'drs' titel wordt afgehaald
één van de belangrijke momenten
waardoor mijn levensloop wordt bepaald

ik heb vier en een half jaar aan mijn proefschrift gewerkt
en ben trots op alles wat er in dit boekje staat
toch vertegenwoordigt het maar een deel
van waar het leven werkelijk over gaat

mijn levensloop omvat het grote geheel
het officiële curriculum vitae toont daarvan slechts een stuk
't omvat degenen die ik liefheb, hoogtepunten, alledaagse dingen, en veel meer
en wordt gekleurd door verdriet en geluk
alles bij elkaar is dat wat het leven inhoud geeft
en maakt dat ik mijn leven volgens haar eigen loop leef.

Jannique

Voor mijn familie

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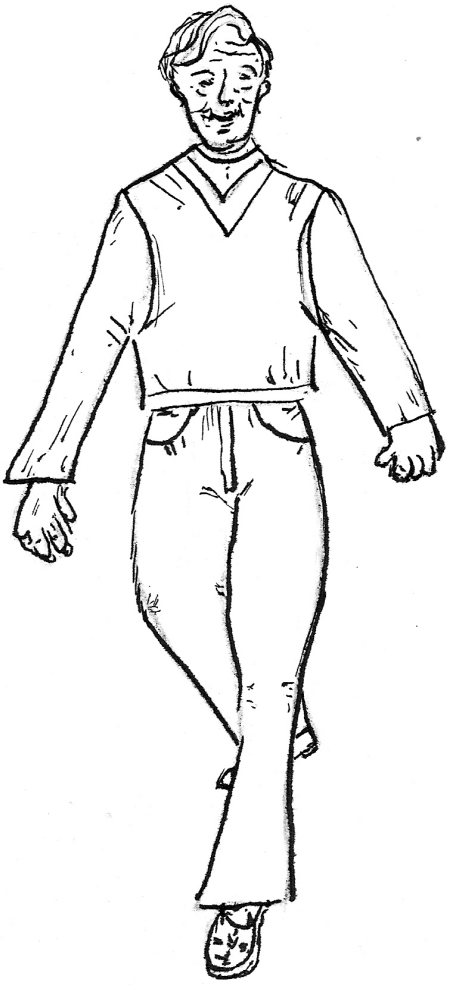
CONTENTS

1

General Introduction



We live in a doubly ageing society: not only is the percentage of older adults within the total population growing, but the life expectancy of these individuals has also increased. In this respect, the promotion of healthy ageing is becoming more important. However, ageing is inevitably linked to cognitive decline. We cannot turn a blind eye to the increasing numbers of adults with age-related health problems, such as cognitive impairment and dementia. In The Netherlands, 175,000 adults aged over 65 years suffer from late onset dementia according to 2002 data. Predictions suggest that this number will further increase from 207,000 in 2010 to 412,000 in 2050, if prevalence rates do not change and curative treatments fail to emerge.[1] Alzheimer's disease is the most common cause of dementia in The Netherlands, responsible for 72 percent of the cases of late onset dementia. The Dutch prevalence rates for Alzheimer's disease correspond to the situation in other European countries.[1] The second and third most frequent causes of dementia are vascular dementia (16 percent) and Parkinson's disease dementia (six percent). In general, the symptoms of dementia are progressively decreasing mental and physical abilities, which cause patients to loose track with reality and become physically dependent, finally leading to loss of autonomy and independence. Because of the severity of the symptoms and the fact that, to date, no curative treatment has become available, dementia is often regarded as the worst case scenario for ageing.

Prior to a diagnosis of Alzheimer's disease, there is a potential transitional stage, in which persons experience memory loss to a greater extent than expected for age and education, but do not meet the criteria for Alzheimer's disease. This stage is referred to as mild cognitive impairment (MCI). A plea was recently made to have MCI included in the Diagnostic and Statistical Manual of Mental Disorders (DSM).[2] As individuals with MCI have an increased risk of developing dementia, this problem can no longer be ignored in clinical and epidemiological research. In light of its high prevalence and the growing number of older adults in the population, it is important that strategies for preventing cognitive decline are developed. The stage of MCI may be the optimum stage at which to intervene.

Two potential beneficial interventions for slowing the rate of cognitive decline are physical exercise and vitamin B supplementation. Because aerobic fitness is positively related to cognition[3], improving fitness by aerobic exercise, which is possible up to very old age[4], may improve cognition in older adults. Similarly, since both normal vitamin B and homocysteine concentrations are positively related to cognition[5], vitamin B supplementation may also help to prevent cognitive decline. Major advantages of exercise and vitamin supplementation are that they can be implemented easily into the daily lives of older adults, and are relatively inexpensive, making them particularly suitable for community-dwelling elderly people.

If proven effective, these interventions would not only have important personal impact for individuals, but they would also have major implications for public health.

This thesis focuses on the effectiveness of a moderate intensity walking program, designed to improve aerobic fitness, and vitamin B supplementation in older community-dwelling adults with MCI. In this general introduction, the concepts of cognition and MCI are explained. In addition, information is provided on hypothesised mechanisms for the relationship between moderate intensity exercise and B vitamins and cognition. This Chapter concludes with an overview of the aims and an outline of the thesis.

Cognition and cognitive decline

According to Lezak (1995), cognition is one of the building stones of human behaviour.[6] The other two are emotionality and executive functions. Cognition deals with the handling of information, emotionality with feelings, and executive functions with the expression of behaviour. Cognition is a broad concept referring to all mental processes that are used to obtain knowledge, or to become aware of the environment, and the use of this knowledge for comprehension and problem-solving. In theory, four major classes of cognition can be discerned: 1) receptive functions - the abilities to perceive information; 2) memory - the ability to learn and remember information; 3) thinking - relating pieces of information; and 4) expressive functions - the functions through which a person expresses him- or herself. In practice, these functions are interwoven. These classes of cognition can be divided in various subclasses, which are described by Lezak (1995)[6] as follows. Receptive functions can be divided roughly into sensation and perception. Sensation is the notification of incoming sensory input; perception is the integration of this input into meaningful data. Lezak (1995) uses the example of the sensation of light falling on the retina being encoded into a pattern, which is recognised as a flower by means of perception. Memory deals with information storage and retrieval. New information is not immediately available in the long term memory. First, large amounts of incoming information are stored for seconds in the registration memory. Then, useful information is transferred to the short-term memory for hours to days. Finally, information is transferred to and stored in the long-term memory. Thinking deals with relating pieces of information to each other by mental processes such as ordering, computation, organising and planning, reasoning, judgment, abstraction, analysis and synthesis. The precise category of thinking is defined by the nature of information being processed (e.g. numbers, words, concepts) and mental processes dealing with that information. Lezak (1995) uses the examples of ‘verbal reasoning’, operations such as ordering and comparing with words, and ‘computation’, operations such as ordering

and compounding with numbers. Finally, expressive functions include all processes by which information is communicated or acted upon, such as speaking, writing, drawing, and facial expressions.

Executive functions, such as planning and problem solving, represent higher order cognitive activities which control and regulate most cognitive functions as described in the previous paragraph. Impairments in executive functions may affect cognitive functions directly. Lezak (1995) explains the difference between cognitive functions and executive functions as follows: "questions about cognitive functions are generally phrased in terms of what or how much (e.g. How much do you know? What can you do?); questions about executive functions ask how or whether a person goes about doing something (e.g. Will you do it, and if so, how?)".

A variety of neuropsychological tests has been developed in order to assess different aspects of cognition. These tests also measure executive functions, as they control cognitive functions. In this thesis, five neuropsychological tests are used. For a description of these tests and their corresponding cognitive domains, see Table 1. In the individual papers in this thesis, referrals to aspects of cognitive function include these cognitive domains, or a more specific neuropsychological focus. Neuropsychological focus is described in the description of the outcome measures in Chapter 3.

Cognitive functions decline as a consequence of the normal ageing process. Besides 'normal cognitive function', the stages 'mild cognitive impairment' and 'dementia' can be distinguished.[7] Cognitive decline is a gradual process and conversion to the next stage occurs when the threshold for that stage is reached, see Figure 1. However, the three stages don't necessarily imply a continuum. As depicted in Figure 1, the course of cognitive decline depends on individual differences in level of cognition (a), age at onset of cognitive decline (b), and rate of cognitive decline (c). The majority of adults aged 65 to 74 do not yet experience cognitive decline, but cognitive decline is found in more than half of adults aged 85 and over.[8,9] Compared with older people who are cognitively healthy, people who will later be diagnosed with Alzheimer's disease show a decline of multiple cognitive functions (e.g. memory, attention, language, visuospatial skills, perceptual speed and executive functions) at an earlier age.[10]

TABLE 1: Description of neuropsychological tests and corresponding cognitive domains

Cognitive domain	Test	Description	Score
Global cognitive function	MMSE[11]	screening tool: cut-off for normal cognitive function, MMSE ≥ 24	0-30 points
Verbal memory	AVLT 15[12]	- immediate recall: 5 trials of recalling a list of 15 words - delayed recall: 1 trial of recalling the list of 15 words 20 minutes after the last administration	- 0-75 words - 0-15 words
Attention	SCWT-A[13]	- word reading: reading 8 rows of 5 words (i.e. blue, green, red, yellow) printed in black - colour naming: naming the colours of 8 rows of 5 coloured rectangles - combination task: naming the colours of the ink of 8 rows of 5 words (blue, green, red, yellow) printed in one of these colours	time (s) to complete each individual task, max. 180
Information processing	DSST[14]	completing boxes with a digit with the corresponding symbol (90 s)	nr. of correctly completed boxes, max. 100
Executive functions	VFT[15]	naming words starting with a given letter during 1 minute, 3 letters per administration	sum of named words

MMSE= Mini Mental State Examination; AVLT= Auditory Verbal Learning Test; SCWT-A= Stroop Colour Word Test-Abridged; DSST= Digit Symbol Substitution Test; VFT= Verbal Fluency Test; s= Seconds; max.= Maximum; nr= Number

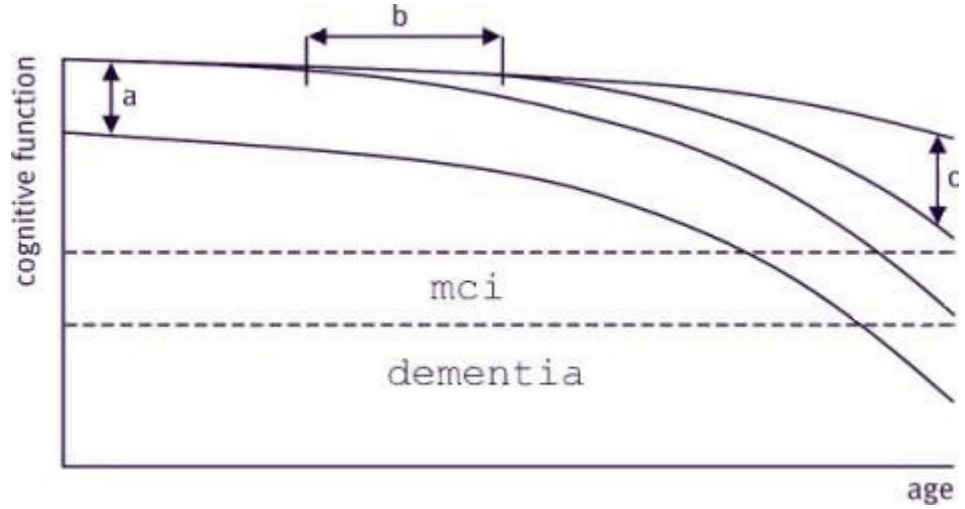


FIGURE 1: Model representing individual differences in level of cognition (a), age at onset of cognitive decline (b), and rate of cognitive decline (c)

dashed lines indicate thresholds for MCI and dementia (reprinted, with permission, from Dik, 2002[16])

Mild Cognitive Impairment (MCI)

Mild cognitive impairment (MCI) refers to subclinical complaints of cognitive function, which do not meet the conventional criteria for dementia. Older adults with MCI experience greater decline than one would expect in the normal ageing process.[17] Episodic memory (memories of a person's own experiences), semantic memory (knowledge unrelated to a person's life) and perceptual speed (ability to quickly and accurately compare letters, numbers, objects, pictures, or patterns) are especially prone to decline.[7] It has been reported that older adults with MCI have an increased risk of developing dementia[7,9,17] and an increased mortality rate[7,18] compared with adults with normal cognitive function.

Disagreement exists about the exact diagnostic criteria for MCI[17], so that the definition of MCI varies considerably across different studies. At the time of development of the study protocol for the randomised controlled trial (RCT) presented in this thesis, the most commonly used criteria were those of Petersen (1999)[19], who characterised MCI on the basis of five criteria: 1) subjective memory complaint; 2) objective memory impairment; 3) normal mental status; 4) intact activities of daily living; 5) no dementia. Different operationalisations of these criteria are however evident in the literature. In a clinical setting, the criteria are determined through clinical judgment.[10] Since this is not feasible in epidemiological (intervention) studies, the inclusion criteria for subjects with MCI in population studies may seem somewhat forced.[20] As a result of these different operationalisations of the MCI criteria, reported prevalences of MCI range from three to 19 percent in the general population.[21] According to the Petersen criteria, the progression rate to Alzheimer's disease in community-dwelling older adults with MCI is 12 percent per year, compared with a rate of one to two percent in adults without MCI.[19] However, the possibility exists that individuals may remain in this stage of MCI or revert to normal cognitive function.[22,23]

In 2004, a subdivision of different kinds of MCI was proposed by Petersen et al.[24] This includes four subtypes of MCI: 1) amnestic MCI, single domain; 2) amnestic MCI, multiple domains; 3) non-amnestic MCI, single domain; and 4) non-amnestic MCI, multiple domains. The clinical subtype of MCI can be identified after a clinician has determined that the individual is neither cognitively healthy, nor demented, and the decline in cognition does not result in impaired activities of daily living. Older people with amnestic MCI have an isolated memory impairment. If the memory impairment is accompanied by impairments in one or more of the cognitive domains, such as language or executive functions, the diagnosis should be amnestic MCI, multiple domains. If not memory, but one of the other domains is impaired, the diagnosis is non-amnestic MCI, single domain.

Finally, non-amnestic MCI, multiple domains is the case if multiple domains, but not memory, are involved. This subdivision has been adopted by the International Working Group on MCI.[10] Amnestic MCI refers to the stage which was previously called MCI, i.e. subjective memory complaints, objective memory impairment, preserved general cognitive function and activities of daily living.[25] If this most recent subdivision is applied to the study population in the present thesis, participants would be categorised as suffering from amnestic MCI. The further distinction between single and multiple domains amnestic MCI could not be made on the basis of the applied inclusion criteria for the RCT described in this thesis.

Physical activity, exercise and cognition

Physical activity comprises any bodily movement, produced by contraction of skeletal muscles, that results in a substantial increase in resting energy expenditure. Exercise is a form of physical activity, referring to planned, structured, and repetitive bodily movement done in order to improve or maintain one or more components of physical fitness.[26] Health related physical fitness refers to the components of fitness that are affected by physical activity and exercise. The construct of health related physical fitness includes the following components: aerobic fitness or cardiorespiratory components (e.g. submaximal exercise capacity, aerobic power); muscular components (power, strength, endurance); motor components (coordination, speed of movement, balance, agility); morphological components (e.g. flexibility, body composition, bone density); and the metabolic components (e.g. glucose tolerance, insulin sensitivity).[27]

In the RCT presented in this thesis, the moderate intensity walking program was designed to improve aerobic fitness. It is therefore considered to be an ‘exercise program’ and more specifically ‘an aerobic exercise program’. The control program, a placebo activity program with low intensity non-aerobic exercise, was not designed to improve aerobic fitness. However, since the program targeted other components of physical fitness such as flexibility and balance, it is also referred to as an ‘exercise program’. In the individual papers presented in this thesis, the term ‘exercise’ is used to refer to the interventions. The term ‘aerobic exercise’ is used only for the walking program. The term ‘physical activity’ is used to describe habitual physical activity levels.

Current Dutch physical activity guidelines for older adults correspond to the international guidelines of being active at moderate intensity (3-5 Metabolic Equivalents) for 30 minutes or more on at least five, but preferably all days of the week.[28]

In The Netherlands, 71 percent of men aged 65-75 years and 63 percent of women in that age group meet this guideline. In older adults aged 75 or over these percentages decrease to approximately 50 percent in men and 40 percent in women.[29]

An overview of prospective observational studies and various trials on the effect of exercise on cognition among cognitively healthy elderly people is provided in Chapter 3.[30] Only one RCT has been conducted to examine the effect of walking on cognition in elderly subjects with MCI.[31] In that study, institutionalised subjects participated three times per week for 30 minutes in low intensity self-paced walking with a walking aid. After six weeks intervention an improvement in executive functions was observed.

A number of reviews and meta-analyses on the effects of physical activity and exercise on cognition in older adults has also been conducted.[32-35] Van Sickle et al. (1996) calculated effect sizes on the basis of 13 intervention studies, including five studies that were not designed as an RCT. Intervention programs included eight aerobic exercise programs, two multicomponent programs with an aerobic component, one non-aerobic exercise program and two interventions were not clearly described. Study populations included both healthy and diseased subjects. Eighty-one effect sizes were calculated, of which 35 fell in the category of small, 28 small to medium, 12 medium to large and six large. On the basis of these effect sizes, it was concluded that exercise promotes modest changes in cognition of older adults. Etnier et al. (1997) performed a meta-analysis including 134 studies with different study designs.[33] Of the 13 studies included by van Sickle et al. (1996), twelve were also included in the meta-analysis by Etnier et al. (1997). In that meta-analysis a small positive effect of long term exercise was observed on cognition in adults aged 60 years or older (effect size [SD]= 0.19 [0.37]). The specific type of exercise was not reported clearly, but on the basis of described mechanisms by which exercise might benefit cognitive function, we assume that the authors refer to aerobic exercise. Moreover, it was not clear how many and from what specific papers this effect size was calculated. Therefore, the correspondence with studies included by van Sickle et al. (1996) could not be determined. Furthermore, on the basis of the provided information, it was not possible to determine the study-design on which these results were based. However, Etnier et al. took the quality of the included studies into account by comparing different categories on the basis of number of threats to internal validity (range 0-5). They concluded that effect size decreased if the methodological quality increased. Colcombe et al. (2003) reviewed 18 intervention studies describing the effect of supervised exercise programs comprising only aerobic training or a combination of aerobic training and strength training.[34] Most trials were executed in community-dwelling, cognitively healthy, but sedentary adults.

Aerobic exercise was found to induce robust selective effects on cognition, in particular executive functions (effect size [SE]= 0.5 [0.03]). Finally, Heyn et al. (2004) reviewed ten randomised trials that examined the effect of any exercise or physical activity program on cognitive function.[35] Study populations included institutionalised and community-dwelling subjects with dementia and related cognitive impairments. Subjects in the intervention groups showed improvements in cognitive tasks compared with those in the control groups (effect size [95 percent confidence interval]= 0.57 [0.38; 0.75]). In general, it was concluded that different types of exercise programs could positively affect cognition.

Considering the age-related decline in participation in moderate intensity physical activities, and the potential beneficial effects of exercise, it would appear that there is a firm empirical basis for prescribing and promoting aerobic exercise among older adults with MCI. Therefore, one of the main hypotheses to be examined in this thesis is that aerobic exercise is beneficial for prevention of cognitive decline in older adults with MCI.

Mechanisms by which aerobic exercise may benefit cognition

Spirduso (2005) has summarised the literature on physiological mechanisms by which aerobic exercise may benefit cognition.[3] She proposed that aerobic exercise affects four major areas of brain function through the improvement of aerobic fitness, as shown in Figure 2. First, exercise may benefit cognition by enhancing cerebrovascular integrity in three ways: 1) maintaining the growth of capillary networks in the brain (angiogenesis); 2) maintenance of cerebral blood flow; and 3) increasing oxygen transport to the brain. Secondly, aerobic exercise might improve cognition by affecting cerebral neurotransmitter balance and function. In the older population, age-related alterations in neurotransmitter synthesis and degeneration occur. It has been suggested that improved aerobic fitness may be associated with a diminution of these changes by stimulating nerve cell regeneration and inducing changes in neurotransmitter synthesis and degradation.[36] For an overview of the literature concerning exercise and neurotransmitters, see Meeusen (2005).[37] Thirdly, aerobic exercise may affect cognition by maintaining neuro-hormonal function. It has been suggested that the neuro-endocrine system accelerates the ageing process through hormonal actions on target brain cells. Staying physically fit may ward off these negative influences by maintaining normal hormonal regulation. Finally, aerobic exercise may induce structural morphological changes in the brain, which may enhance cognition. These four areas of brain functioning are hypothesised to overlap and interact with each other.[3] As a result, modulations in one of these areas would affect the other three.

Most research in this field is based on animal studies. For overviews of the animal literature examining the relation between aerobic fitness, ageing and cognition, see McAuley (2004) and Kramer (2005).[38,39] However, in humans, changes in cognition must be mediated by changes in brain activity and morphology. Colcombe et al. (2004) were pioneers in examining the effect of aerobic exercise training on brain activity in humans.[40] They carried out an RCT in a sample of 29 highly-fit community-dwelling adults with a mean age of 66 years. Subjects randomised to the aerobic exercise group walked three times per week for six months. The program was designed to improve aerobic fitness. Session duration was initially 10-15 minutes, increasing to a maximum of 45 minutes. Intensity started at 40 percent of heart rate reserve and increased to 70 percent during the program. The control group participated in a stretching and toning program with the same frequency and duration. After six months, there was increased function of particular areas of the brain during a cognitive challenging task in the intervention group, compared with the control group. The authors considered it encouraging that their findings in humans were consistent with the findings in animal literature on ageing and cognition. Considering its importance and complexity, the study of mechanisms by which aerobic exercise benefits cognition in humans will remain a central focus of interest in future studies.

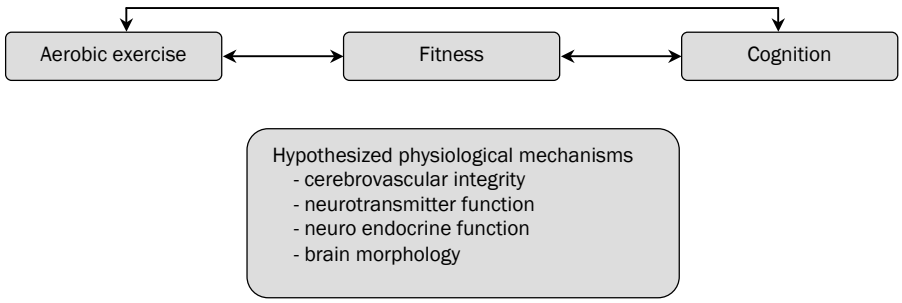


FIGURE 2: Conceptual model for the relation between aerobic exercise and cognition
(adapted from Spirduso et al., 2005[3])

Vitamin B supplementation and cognition

B-vitamins are obtained from the diet. For example, folic acid is obtained from green vegetables, citrus fruits, liver and whole grains; vitamin B12 from animal-origin sources such as meat, fish, eggs, dairy; and vitamin B6 from meat, fish, whole grains, eggs, vegetables, bananas and milk. B vitamins play an important role in the metabolism of homocysteine, which is a product in the metabolism of the amino acid methionine.

Folic acid, vitamin B12 and vitamin B6 are essential for transforming homocysteine to methionine. Low concentrations of these vitamins are relatively common in older adults and cause increased homocysteine concentrations. Vitamin B supplementation reduces homocysteine concentrations.[41]

An overview of associations between vitamin B, homocysteine and cognition, is provided in Chapter 3.[30] In short, low concentrations of folic acid, vitamins B12 and B6 and increased homocysteine concentrations are negatively associated with cognitive performance. Moreover, increased homocysteine concentrations are a strong independent risk factor for the development of dementia and Alzheimer's disease.[42]

In 2003, Malouf et al. conducted three systematic reviews on the effect of vitamin B supplementation on cognition.[43-45] In the review on folic acid, with and without vitamin B12, for cognition four double-blind placebo controlled trials were included.[44] One RCT was carried out among cognitively healthy subjects. The other three RCT's enrolled cognitively impaired and demented subjects, with or without folate deficiency. Sample sizes ranged from 30 to 211 subjects. Doses of folic acid ranged from 750 micrograms to 15 milligrams per day and the intervention periods lasted from five to twelve weeks. In one study a combination of folic acid and vitamin B12 was given. Folic acid with and without vitamin B12 was effective in reducing homocysteine concentrations. However, no effects on cognition were observed. Only two double-blind RCT's were included in the review on vitamin B12 supplementation for cognition.[43] In both studies older adults with dementia and low concentrations of vitamin B12 were included. In one study, 31 subjects were included and three groups were compared: a group receiving 10 micrograms vitamin B12 daily for one month; a group receiving 50 micrograms; and a control group. In the other study 11 subjects were included. Five of them received injections of 1000 micrograms of vitamin B12 daily for five days, followed by one injection per month for five months. No cognitive benefits of vitamin B12 supplementation were observed. The third review dealt with the effect of vitamin B6 supplementation on cognition.[45] Two double-blind RCT's were included. Both trials were carried out in cognitively healthy older adults. In one study, twelve women received 75 milligrams vitamin B6 daily, for five weeks. In the other study, 38 men received 20 milligrams of vitamin B6 per day, for 12 weeks. In line with the other two reviews no beneficial effect on cognitive function was observed.

Since publication of these reviews, seven double blind RCT's on the effect of vitamin B supplementation on cognition have been published.[46-52] Only Durga et al. (2007) observed a beneficial effect. The intervention involved three years supplementation with 800

micrograms folic acid on memory, information processing speed and sensorimotor speed, in 818 subjects with increased homocysteine and normal vitamin B12 concentrations.[46] Interventions in the other six recent trials included single administration and combinations of folic acid, vitamins B12 and B6. Interventions lasted from three months to two years. Sample sizes ranged from 140 to 276 subjects.

The findings of these studies are not encouraging. However, it must be noted that most studies were not conducted among subjects with MCI, half the published studies included few subjects, and only three studies had an intervention of one year or longer.[46,48,49] The combination of B vitamins was only examined in two studies.[48,51] In contrast, the RCT described in this thesis includes a relatively large number of participants with MCI and differs from previous studies with respect to duration of the intervention, and the vitamin supplement. Therefore, the other main hypothesis to be examined in this thesis is that supplementation with a combination of folic acid, vitamin B12 and vitamin B6 is beneficial for cognitive function in older adults with MCI.

Mechanisms by which vitamin B supplementation may benefit cognition

Calvaresi and Bryan (2001) hypothesised that a combination of folic acid, vitamin B12 and B6 may affect cognitive performance via two interrelated mechanisms: 1) a direct and possibly acute influence via hypomethylation; and 2) a longer term positive influence on homocysteine concentrations, resulting in structural vascular changes in the brain.[5] The potential effects of vitamin B supplementation on cognition through these mechanisms is represented in Figure 2. The hypomethylation hypothesis deals with the direct effects of a lack of methionine on the central nervous system. In the case of low concentrations of folic acid, vitamins B12 and B6, homocysteine cannot be transformed to methionine. Thus, homocysteine concentrations increase and hypomethylation occurs. A lack of methionine inhibits many reactions in the central nervous system, finally resulting in disorders in the functions and synthesis of substances such as neurotransmitters, which are crucial to neurological and psychological status. Therefore, sufficient B vitamins are needed in order to keep the processes of the central neural system going. The homocysteine hypothesis[5], proposes an indirect long term effect of vitamin B supplementation on cognition by preventing detrimental cerebrovascular changes through normalising homocysteine concentrations. Increased homocysteine concentrations are associated with vascular damage, and cerebrovascular changes in turn appear to have a negative effect on cognitive function. Vitamin B supplementation may preserve and protect cognitive function through decreasing the risk of cerebrovascular damage by lowering homocysteine concentrations.

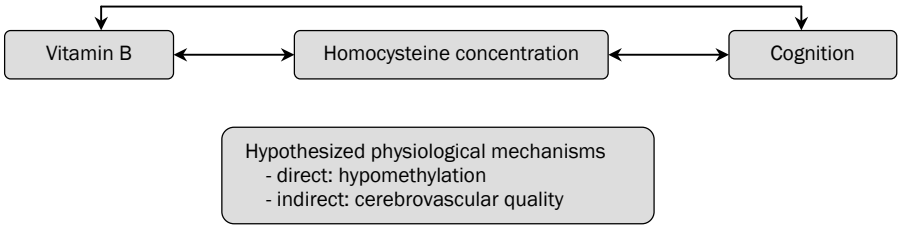


FIGURE 3: Conceptual model for the relation between vitamin B supplementation and cognition

Aerobic exercise, vitamin B supplementation and cognition

The models represented in Figures 2 and 3 have minimal overlap in terms of the hypothesised relations between aerobic exercise and vitamin B supplementation with cognition. Therefore, since there appears to be little biological explanation for a possible interaction between aerobic exercise and vitamin B supplementation, the RCT described in this thesis was not powered to examine such an interaction effect. Consequently, both interventions were considered to be independent.

Overall aim and outline of the thesis

The main aim of the work described in this thesis was to examine the effects of moderate intensity aerobic exercise and vitamin B supplementation on cognition in older adults with cognitive decline. In order to do so, an RCT was conducted entitled Project FACT: Folate physical Activity Cognition Trial. It was hypothesised that: 1) moderate intensity walking is beneficial for prevention of cognitive decline in community-dwelling older adults with mild cognitive impairment; and 2) supplementation with folic acid, vitamins B12 and B6 is beneficial for prevention of cognitive decline in community-dwelling older adults with MCI. Secondary aims were to address the impact of each intervention on quality of life, daily physical activity levels and aerobic fitness, and homocysteine and vitamin B concentrations.

Chapter 2 comprises a systematic literature review. In this review, the effects of different types of physical exercise programs on cognitive function of subjects with and without cognitive decline are compared, and the methodological quality of included RCT's is determined and discussed.

Chapter 3 describes the study design and research protocol in detail. It provides an extensive description of study background and objectives, the recruitment procedure for the participants and details on the interventions and the outcome measures. Project FACT is designed as an RCT with a two-by-two factorial design. The advantage of a factorial design is the efficient use of the study population for assessing the effects of two interventions at the same time. It also allows for exploration of additive effects, though Project FACT was not powered to examine interaction between aerobic exercise and vitamin B supplementation.

Chapter 4 describes the two-step population screening method developed for the recruitment of older adults with MCI from the general population, whereby the applied screening method by questionnaire and telephone was compared with a face-to-face assessment. The rate of agreement in classifying participants as having MCI using the two methods was determined. Eligible subjects who were not available for participation at the start of Project FACT, predominantly because of holidays, were approached six months later for participation in the telephone interview. For practical and logistical reasons, these subjects were not included in the RCT. Since they were included in the description of the two-step population screening, the number of subjects reported in Chapter 4 exceeds the number of randomised participants as described in Chapter 5.

Chapter 5 describes the effect of a moderate intensity walking program designed to improve aerobic fitness, and vitamin B supplementation, on multiple outcomes. Chapter 5.1 focuses on the primary outcome measure, i.e. cognitive function. In Chapter 5.2, the effects on quality of life are described. Chapter 5.3 provides an evaluation of the feasibility of the walking program and describes the effect on aerobic fitness and daily physical activity levels. Chapter 5.4 focuses on the effect on concentrations of homocysteine and vitamin B in blood. Chapters 5.1-5.4 were written as separate articles for publication in scientific journals. Therefore some overlap between these Chapters exists.

In Chapter 6, the main findings of this thesis are summarised and discussed with respect to strengths and limitations of the study. Moreover, findings are placed in a broader perspective of current knowledge. Finally, recommendations for future research and implications for public health are given.

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2

Physical exercise interventions and cognition: different effects in elderly people with and without cognitive decline? a systematic review

JGZ van Uffelen, MJM Chin A Paw, M Hopman-Rock, W van Mechelen
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ABSTRACT

Background

In an ageing society, it is of importance to develop interventions that may prevent cognitive decline. From the literature it emerges that physical exercise may benefit cognition. The aim of this review is to determine whether the effects of exercise on cognition differ between subjects with and without cognitive decline.

Methods

Randomised controlled trials were identified by literature searches in Pubmed, Embase, CENTRAL, PsycINFO and Ageline. Papers were included on the basis of predefined inclusion criteria. Two independent reviewers assessed methodological quality according to a standardised Delphi list. Furthermore, data on study populations, exercise interventions, and effectiveness were extracted.

Results

Twenty-one studies were included, of which six among subjects with cognitive decline. Maximum achievable quality score was nine points. Quality scores of included studies ranged from one to seven (mean score: 3.7). In 12 studies, no significant intervention effect was observed. In nine studies, including four among subjects with cognitive decline, a significant beneficial effect was observed of aerobic training (n= 6) or strength training (n= 3) on information processing, executive functions and memory in cognitively healthy elderly and on global cognition and executive functions in elderly with cognitive decline.

Conclusions

The included trials showed moderate effectiveness of exercise for cognition. However, quality of included studies was poor. More studies of good methodological quality are urgently needed to replicate findings. Furthermore, future research should address the most appropriate design of exercise programs, in terms of type, intensity, frequency, and duration, in combination with feasibility for specific populations with and without cognitive decline.

INTRODUCTION

The prevalence of age-related health problems, such as cognitive impairment and dementia, increases with age. At the individual level, cognitive decline places a burden on subjects and their significant others, because of the detrimental effect on quality of life[1] and the association with a higher risk for functional limitations and disability.[2,3] At the population level, cognitive decline, and especially dementia, put an enormous burden on healthcare systems in terms of finances and manpower. Obviously, effective interventions for slowing down cognitive decline would greatly benefit both the individual and society. In this respect, a number of systematic reviews and meta-analyses reported small beneficial effects of physical activity and exercise on cognition in cognitively healthy older adults[4-6] and adults with cognitive impairment and dementia.[7-9] No links were established yet between study populations with and without cognitive decline.

Three stages of cognition can be distinguished, i.e. normal cognitive function, mild cognitive impairment and dementia.[10] In the stage of normal cognitive function, cognition declines as a normal consequence of the ageing process. Mild cognitive impairment (MCI) refers to the in-between stage in which a person experiences cognitive decline which is more serious than is expected on the basis of the normal ageing process, but does not meet criteria for dementia.[11] Although subjects with MCI have an increased risk to develop dementia[10,12], the possibility exists that they remain in the stage of MCI or revert to normal cognition.[13,14] Dementia of the Alzheimer type is a syndrome marked by memory impairment and impairment in at least one other domain, such as aphasia, apraxia, agnosia or disturbances in executive functions.[15] Dementia goes together with irreversible progressive cognitive decline and leads to significant impairment in social functioning.

Various potential mechanisms for the enhancing effect of exercise on cognition have been hypothesised. In a systematic review on longitudinal studies exploring the effect of physical activity on cognition and dementia, Fratiglioni et al. (2004) abstracted three hypotheses.[16] The cognitive reserve hypothesis assumes that physical activity and exercise improve the non-neural components of the brain, resulting in increased perfusion of the brain, which in turn leads to larger cognitive reserve. The vascular hypothesis presumes that exercise reduces the risk of cardiovascular disease, which is a determinant of dementia. Finally, the stress hypothesis poses that exercise benefits cognition by decreasing stress since subjects susceptible to stress have a two-fold risk for dementia.

The aim of this systematic review is to summarise randomised controlled trials examining the effect of exercise programs on cognition in older adults. In addition to previous reviews, a distinction is made between adults with and without cognitive decline.

METHODS

Literature search

The databases Pubmed, Embase, CENTRAL (Cochrane Central Register of controlled trials), PsycINFO and Ageline were searched for relevant studies in February 2007. Groups of thesaurus terms as well as free terms were used to search the databases. Terms for older adults (thesaurus terms OR elderly, seniors, aging, or ageing) were used in AND-combination with terms for exercise (thesaurus terms OR exercise*, physical activity, physical training, strength training, resistance training, aerobic training, cardiovascular training, endurance training, flexibility training, relaxation, Tai Chi, walking, or yoga) and search terms representing cognition, cognitive processes, cognitive decline or dementia (thesaurus terms OR cogniti*, memory, executive function*, or executive control). Search results were limited by search terms for specific study design, e.g. clinical trial. Detailed search profiles can be obtained through a request to the second author.

Inclusion criteria and selection process

In order to be included in the review, studies had to meet the following criteria: 1) design - randomised controlled trial; 2) population - cognitively healthy older adults or adults with cognitive decline or dementia, but no mental disorders other than dementia, such as depression; 3) intervention - physical exercise program; 4) outcome - cognitive function measured using neuropsychological tests. Only full-text articles written in English were included. Titles, keywords and abstracts of articles identified through the search process were reviewed to identify eligible papers. Checking for eligible papers was done first by JvU to exclude articles out of scope. Subsequently, the first and second author (JvU and MC) independently reviewed all potentially relevant references for eligibility. In the case of doubt or absence of an abstract, the full paper was retrieved.

Data extraction and methodological quality

Data on the study population, exercise programs and outcome measures were extracted by JvU and MH. On the basis of program descriptions in the individual studies, programs were qualified as aerobic, strength, flexibility or balance training, or combinations thereof. Methodological quality of the included studies was independently determined by two reviewers (JvU and MC) using the Delphi list developed by Verhagen et al.[17], which has been

used in a previous review on exercise interventions in the elderly.[7] This list consists of nine quality criteria assessing different methodological aspects, see Table 1. Criteria have a 'yes' (= 1), 'no' (= 0) or 'unclear' (= 0) answer format. Disagreements between reviewers were discussed and resolved. All criteria have the same weight, and a quality score ranging from zero to nine was calculated for each study by summing scores for individual Delphi items. In accordance with previous reviews, high quality was defined as a score of five or higher.[18]

TABLE 1: Criteria considered for quality assessment according to Verhagen et al.[17]

1a. Was a method of randomisation performed?
1b. Was the treatment allocation concealed?
2. Were the groups similar at baseline?
3. Were the eligibility criteria specified?
4. Was the outcome assessor blinded?
5. Was the exercise trainer blinded?
6. Was the subject blinded?
7. Were point estimates and measures of variability presented for the primary outcomes?
8. Did the analysis include an intention-to-treat analysis?

Distinction between study populations with and without cognitive decline

Two study populations are distinguished in the results: cognitively healthy adults and adults with cognitive decline. Cognitive decline was determined on the basis of the description of the population or the provided MMSE-scores. In the latter case, the standard cut-off point of 24 was applied.[19] If no specific information about cognitive status was reported, it was assumed that the population was cognitively healthy.

RESULTS

Study selection

The literature searches yielded a total of 1062 potentially relevant articles: 462 in Pubmed, 415 in Embase, 134 in CENTRAL, 13 in PsycINFO and 38 in Ageline. After removing references which were selected from more than one database, 827 articles were left. After removing papers out of scope, the titles and abstracts of 65 references were finally checked for eligibility by JvU and MC. Twenty-two references met the inclusion criteria after checking

titles and abstract. The abstracts of six articles provided insufficient information to make a decision. Therefore, 28 full text articles were retrieved in order to screen the full text. Seven papers were excluded after all, because of the following reasons: no RCT (n= 1); study population also including subjects with depression and psychosis (n= 1); no isolated exercise intervention, but a multi-component intervention including exercise (n= 2); wrong outcome measures (n= 2); or describing same study and results as one of the included studies (n= 1). Finally, 21 papers were included.[20-40]

Methodological quality

Methodological quality of the included papers is summarised in Table 2. Quality scores ranged from one to seven out of the nine points to be achieved maximally. It must be remarked that the score of one point for the study of Kramer[25] presumably is not representative of the actual methodological quality, but rather is the result of the restricted number of words for publication in that journal, i.e. Nature. Therefore, this study is not further considered in this section. Overall, the quality of the trials was poor with a mean quality score of 3.7, mainly because of insufficient information reported in the papers. Only five of the studies achieved a score of five or higher and were qualified as high quality studies.[20,26,29,32,39] All studies used randomisation, but only five of the studies described that treatment allocation was concealed.[20,26,32,36,39] Despite randomisation, groups were not comparable at baseline in five studies.[22,24,30,35,36] One study did not report on baseline comparability.[27] In three of the 14 studies reporting that study groups were similar at baseline, the number of subjects per group was only ten or less[20,23,31] or 15[38,39] making finding statistically significant differences difficult. Seven studies did not specify the eligibility criteria.[22,23,27,32-34,40] If only exclusion criteria were reported, this item was rated as 'unclear'. In general, blinding was not consistently described. Of the 60 items on blinding, only 24 could be filled out on the basis of information provided in the individual papers, of which eight items scored 'yes'. In six studies, the outcome assessor was blind.[20,28,29,31,32,35] Subjects were blinded in one study.[37] The exercise trainer was also blinded in one study.[26] Ten studies analysed the data on an intention-to-treat basis for those with complete data.[20,21,27-29,32-34,38,39] Only two studies[20,26] reported point estimates and measures of variability for the between group differences in outcome measures.

Study populations

The details of the study populations are summarised in Table 3. The sample sizes varied from 20 to 210 subjects: 11 studies included 50 subjects or less and six studies included more than 100 subjects. The mean age of the study populations ranged from 64 to 88 years. The majority of subjects were women. One study did not report on the gender of the

subjects.[25] Two studies reported to be performed in demented adults[36,39] and one study in subjects with mild cognitive impairment.[35] In the other studies, cognitive status was not explicitly described. However, if the usual cut-off point of 24 points on the MMSE for cognitive decline[19] is applied to the provided mean MMSE-scores, cognitive decline is expected in three more studies.[20,28,29]

Exercise programs

The exercise programs are summarised in Table 4. Eight programs comprised aerobic training only[21,23-25,27,31,32,36] and four programs covered strength training only.[26,31,34,38] Ten studies included an aerobic or strength component combined with flexibility and/or balance training.[20,22,28-30,33,35,37,39,40] If only considering the six studies among subjects with cognitive decline or dementia, two comprised aerobic training only[35,36]; two programs consisted of strength + flexibility training[20,28]; and two covered strength + flexibility + balance training.[29,39]

Intensity of aerobic training programs or the aerobic component in all-round programs (n= 14 together) was operationalised in various ways: 60-70 percent of heart rate reserve (HRR) (n= 3)[27,31,37]; 30-40 percent of HRR (n= 1)[37]; 70 percent of maximum heart rate (n= 3)[21,22,32]; Ratings of Perceived Exertion-scale (n= 1)[24]; ventilatory threshold (n= 1).[23] Five studies did not report on specific intensity[25,33,35,36,40], including the only study on aerobic training in demented elderly people.[36] The strength training programs and all-round programs including a strength training component (n= 13) comprised progressive resistance training (n= 8)[20,22,26,28,29,31,38], or did not report on progression (n= 5).[31,33,34,39,40] Resistance machines were used in two strength training programs.[34,38]

The intervention duration ranged from six weeks to one year (mean duration: 20 weeks). The majority of the programs was performed three times a week (n= 11).[20-22,24,26,27,30,35-38] Three programs were performed once a week[32,34,39], in one of these studies additional individual exercise was explicitly encouraged.[32] Five programs were performed twice a week[23,28,29,33,40]; one program five times per week[31]; and for one study frequency was not reported.[25] Session duration varied from 30 to 60 minutes (n= 17) (mean: 48 minutes), and was not reported in four studies.[24,25,34,38]

The ample majority of studies examined group-based exercise programs (n= 16). Two studies did not report on this issue[25,34] and three studies examined an individually based program.[24,26,35] Most exercise intervention programs in subjects with cognitive decline were group-based (n= 5)[20,28,29,36,39], one study did not report whether the intervention was group-

based.[35] Despite the fact that almost all programs were group-based, specification of exercise instructors of these programs was only mentioned in nine studies. Exercise sessions were supervised by: physical therapists (n= 3)[28,30,39]; trained exercise leaders (n= 4)[31-33,37,40]; exercise physiologist (n= 1)[20], or the researcher (n= 1).[36]

Dropout and attendance

Dropout from the study, defined as no post-intervention measurements available, was reported in 17 studies including five studies performed in subjects with cognitive decline.[20,28,29,36,39] In cognitively healthy subjects, drop-out ranged from 0-28 percent (median [25th; 75th percentile]= 6 [0-18] percent). In subjects with cognitive decline, the range was 0 percent to 38 percent (median [25th; 75th percentile]= 15 [2; 35] percent). Mean attendance at the exercise intervention classes was reported in 12 studies[20-22,26-30,32,33,38,40] including three in subjects with cognitive decline[20,28,29] and ranged from 69-96 percent in cognitively healthy adults and 72-80 percent in subjects with cognitive decline. Of these 12 studies, seven included a control program with session attendance ranging from 56-100 percent.[20-22,27-29,32] In most studies, it was not described whether dropouts were included in the attendance rates. Two studies reported that only subjects attending 70 to 75 percent of the sessions were included in their analyses.[36,37]

Effectiveness

The large range of neuropsychological tests used in the 21 selected trials to assess cognition and the effectiveness are described in Table 5. Twelve studies found no significant beneficial effect of exercise on cognition in cognitively healthy adults (n= 10)[21-23,26,27,32-34,37,38],or in adults with cognitive decline (n= 2).[28,29] Nine trials did observe a beneficial effect on some of the used measures of cognition; five among cognitively healthy subjects[24,25,30,31,40] and four among subjects with cognitive decline.[20,35,36,39] In cognitively healthy adults, improvements were observed in memory (face recognition, digit span)[24,40], information processing abilities (organisation, auditory processing)[31] and executive functions (task switching, response compatibility, stopping tasks, fluency).[25,30] The effective exercise programs included mainly aerobic training or all-round programs with an aerobic component.[24,25,31,40] One study observed a beneficial effect of strength training.[30] In subjects with cognitive decline, improvements were observed in global cognitive function (MMSE)[20,39] and executive functions (category fluency, trail making, clock drawing).[35,36,39] Exercise programs in these studies included aerobic training (n= 2)[35,36] and strength training (n= 2).[20,39] Duration of these programs ranged from 6-52 weeks; session frequency was three times per week in three studies and once per week in one study. Two strength programs observed near significant benefits of strength training on memory in cognitively healthy subjects (immediate + delayed recognition, p= 0.07 and p= 0.08) [34], and on global cognitive function in subjects with cognitive decline (MMSE, p= 0.06).[28]

TABLE 2: Quality assessment of randomised controlled exercise trials in older adults in different stages of cognitive function.

First author, year	1a. Rando-misation ?	1b. Treatment allocation concealed?	2. Group similarity at baseline?	3. Specified eligibility criteria?	4. Blinded outcome assessor?	5. Blinded exercise trainer?	6. Blinded subjects ?	7. Point estimates/ measures of variability?	8. Intention-to-treat analysis?	Score
Baum, 2003[a]	Y	Y	Y	Y	Y	?	N	Y	Y	7
Blumentahl, 1991	Y	?	Y	Y	?	?	N	N	Y	4
Emery, 1990	Y	?	N	?	?	?	N	N	N	1
Fabre, 2001	Y	?	Y	?	?	?	N	N	?	2
Hassmen, 1997	Y	?	N	Y	?	NA	?	N	?	2
Kramer, 1999	Y	?	?	N	?	?	?	N	?	1
Lachman, 2006	Y	Y	Y	Y	?	Y	N	Y	?	6
Madden, 1989	Y	?	?	?	?	?	?	N	Y	2
McMurdo, 1994[a]	Y	?	Y	Y	?	N	?	N	Y	4
McMurdo, 2000[a]	Y	?	Y	Y	Y	?	?	N	Y	5
Molloy, 1988	Y	?	N	Y	Y	?	N	N	?	3
Moul, 1995	Y	?	Y	Y	?	?	?	N	?	3
Oken, 2006	Y	Y	Y	?	Y	?	N	N	Y	5
Okumiya, 1996	Y	?	Y	N	Y	?	N	N	Y	4
Perrig Chiello, 1998	Y	?	Y	N	?	?	N	N	Y	3
Scherder, 2005[a]	Y	?	N	Y	Y	?	N	N	?	3
Stevens, 2006[a]	Y	Y	N	Y	?	N	N	N	N	3
Stevenson, 1990	Y	?	Y	Y	?	?	Y	N	N	4
Tsutsumi, 1997	Y	?	Y	Y	?	?	N	N	Y	4
Van de Winkel, 2004[a]	Y	Y	Y	Y	N	N	?	N	Y	5
Williams, 1997	Y	?	Y	?	?	?	?	N	N	2

[a] Study among subjects with cognitive decline; NA= Not Applicable; Y= Yes; N= No; ?= Unclear

TABLE 3: Description of study populations

Author, year	- Number of subjects (n)[b]; gender (%women); mean age (SD) and/or range - Baseline cognitive status (if available)	Eligibility criteria
Baum, 2003[a]	- n= 20; 75% ; 88 yrs, range 75-99 - mean MMSE 21; range 10-29; 50% MMSE ≤ 21	- inclusion: age ≥ 65; residents of a long term care facility, assisted living + nursing home for ≥ 3 months; ability to ambulate alone, with assistive devices or one caregiver. - exclusion: unstable acute or chronic illness; inability to follow a two-step command; assaultive behaviour pattern; not wanting to discontinue any current physical therapy.
Blumenthal, 1991	- n= 101; 50%; 67 yrs, range 60-83 - healthy adults; no MMSE	- inclusion: age ≥ 60; healthy and free from coronary disease; not participating in regular exercise.
Emery, 1990	- n= 48; 83%; 72(6) yrs, range 61-86 - no MMSE	- inclusion: living in inner-city community; not participating in regular exercise.
Fabre, 2002	- n= 32 ; 84% ; 66(2) yrs, range 60-76 - healthy adults without signs of dementia; no MMSE	- inclusion: member of club (?); age ≥ 60. - exclusion criteria: depression; positive ECG during exercise testing; no breathing through mouth during testing; disease during training.
Hassmen, 1997	- n= 40; 50%; 66 yrs, range 55-75 - healthy adults; no MMSE	- inclusion: no self-reported medical problems or impairments; no use of medication in past 6 months; not participating in regular exercise.
Kramer, 1999	- n= 124; ?; range 60-75 yrs - no MMSE	- inclusion: sedentary adults.
Lachman, 2006	- n= 210; 78%; 75 (7) yrs, range 60-94 - no MMSE	- inclusion: age ≥ 60; community-dwelling; sedentary; limitations in minimal 1 of 9 physical function areas of Short Form-36 physical function scale. - exclusion: contraindications for exercise; current treatment for cancer; kidney disease requiring dialysis; recent fracture; uncontrolled diabetes or seizures; regular use of wheelchair; current rehabilitation case; current fainting or dizzy spells; sudden loss of coordination; blindness.
Madden, 1989	- n= 85; 48%; 67 (4) yrs, range 60-83 - no MMSE	- exclusion: uncontrolled hypertension; diabetes; heart disease; taking beta blockers or psychotropic medicine; contraindications for exercise.
McMurdo, 1994[a]	- n= 65; 83%; 83 (8) yrs, range 67-98 - mean MMSE (SD)= 15 (4)	- inclusion: resident of home for the elderly; ability to toilet, dress, walk independently. - exclusion: severe communication difficulties.
McMurdo, 2000[a]	- n= 133; 81%; 84(7) yrs, range 70-97 - mean MMSE (SD)= 19 (6)	- inclusion: resident of home for the elderly; age ≥ 70. - exclusion: MMSE < 12.
Molloy, 1988	- n= 50; 100%; 83 yrs, range 73-90 - mean MMSE (SD)= 25 (5)	- inclusion: women; resident nursing home; women; age ≥ 70; ability to walk without assistance; no disability or disease that compromised ability to exercise.
Moul, 1995	- n= 30; 63%; 69 (1) yrs, range 65-72 - no MMSE	- inclusion: no current symptoms or signs suggestive of heart disease; < 2 moderate or vigorous aerobic or resistance training sessions > 20 min/week; permission from physician to participate.
Oken, 2006	- n= 135; 75%; 72 (5) yrs, range 65-85 - healthy adults; no MMSE	- exclusion: actively practicing yoga or tai-chi in last 6 months; performing aerobic exercise > 210 min/week; insulin-dependent diabetes; uncontrolled hypertension; evidence of liver or kidney failure; significant lung disease; alcoholism or drug abuse; symptoms or signs of congestive heart failure; symptomatic ischemic heart disease; significant valvular disease; significant visual impairment.
Okumiya, 1996	- n= 42; 57%; 79 (5) yrs, range 75-87 - mean MMSE (SD)= 28 (3)	- inclusion: age ≥ 75; community-dwelling.
Perrig Chiello, 1998	- n= 46; 39%; 73 yrs - no MMSE	- inclusion: subjects from Longitudinal Interdisciplinary Aging Study, interested in resistance training.

Scherder, 2005[a]	- n= 43; 88%; 86 (5) yrs, range 76-94 - mild cognitive impairment; 12 item MMSE ≥ 7	- inclusion: resident of combined home for the elderly/ nursing home; 12 item MMSE 7-10 indicating mild/moderate cognitive deterioration OR 12 item MMSE 11-12 + decreased memory performance; meeting MCI-criteria. [11] - exclusion: probable AD; history of alcoholism; cerebral trauma; hydrocephalus; neoplasm; epilepsy; disturbances of consciousness; focal brain disorders.
Stevens, 2006[a]	- n= 75; 75%; 81 yrs - demented ; 9 ≤ MMSE ≤ 23	- inclusion: resident aged care facility; mild to moderate dementia OR 9 ≤ MMSE ≤ 23; physically capable of gentle regular exercise; able to respond to verbal and physical response.
Stevenson, 1990	- n= 72 ; 55% ; 64 (4) yrs, range 60-81 - healthy adults; no MMSE	- inclusion: age ≥ 60; community-dwelling; absence of cardiovascular disease, hypertension, diabetes; normal findings in physical examinations + blood tests; absence of coronary disease; normal echocardiogram; no abnormal findings on cycle ergometer stress test.
Tsutsumi, 1997	- n= 42; 79%; 69 (6) yrs, range 61-86 -healthy adults; no MMSE	- inclusion: age ≥ 60; community dwelling; medically healthy; no regular exercise in past 6 months. - exclusion: cardiovascular disease; taking medication for hypertension.
van de Winckel, 2004[a]	- n= 25; 100%; 82 (4) yrs - demented (AD n= 22; MID n= 3); mean MMSE (SD)= 12 (5).	- inclusion: hospitalised patients with dementia; MMSE score < 24; able responding to requests; able to mimic movements; able hearing music. - exclusion: apathetic patients; inability to maintain seated position for 30 minutes.
Williams, 1997	- n= 187; 100%; 72 (5) yrs - no MMSE	- inclusion: community dwelling; age ≥ 60; took part in initial phase of Randwick falls and fractures study. - exclusion: ill; immobile; hospitalised; medical condition involving neuromuscular, skeletal or cardiovascular system precluding taking part in exercise; attending exercise classes with intensity equivalent to intervention.

AD= Alzheimer's disease; GDS= Geriatric Depression Scale; MID= Multi Infarct Dementia; MMSE= Mini Mental State Examination; SD= Standard Deviation;

[a] Study among subjects with cognitive decline; [b] Number as reported in abstract

TABLE 4: Description of exercise programs and session attendance

Author, year	Program (P); Intensity (I); Frequency + Duration (F/D); Organisation + Supervision (O/S) vs. Comparison[c]	Mean attendance (SD)
Baum, 2003[a,b]	P: strength + flexibility training. I: starting with ROM without resistance, progressing to 1 set of 5 repetitions, and 2 sets of 10 repetitions, using balls, soft ankle and wrist weights and therabands. F/D: 52 wks, 3 x/wk, 60 min. O/S: group-based, exercise physiologist. vs. recreational group with art therapist/ social worker, activities such as drawing, playing cards.	SFT: 80% C: 56%
Blumenthal, 1991[b]	P: aerobic training. 10 min warm-up; 30 min bicycle ergometry + 15 min brisk walking or jogging with supplemented arm ergometry for 5 min; 5 min cool-down. I: 70% Hrmax. F/D: 16 wks, 3x/wk, 60 min. O/S: group-based, ? vs. non-aerobic yoga training: I: low. F/D: 16 wks, 2x/wk, 60 min. O/S: group-based, ? vs. waiting list control group.	AT: 96% Yoga: 100% NIC: NA
Emery, 1990	P: aerobic + strength + flexibility training. 15 min warm-up; 25 min aerobic walking + muscle strengthening; 5 min cool-down. I: 70% Hrmax (220- age) + increasing no of reps. F/D: 12 wks, 3x/wk, 60 min. O/S: group-based, ? vs. social activity control group + waiting list control group (pooled in analyses).	ASFT: range 61-94% C: range10-94%
Fabre, 2002	P: aerobic training. 5 min warm-up; 45 min interval training (brisk walking, jogging); 10 min cool-down. I: individualised conform heart rate (ventilatory threshold). F/D: 8wks, 2x/wk, 60 min. O/S: group-based, ? vs. comparison (factorial design): mental training (8 wks, 1x/wk, 90 min), aerobic + mental training, social activity control group.	AT: 'very good' C: 'very good' (non-attenders excluded)
Hassmen, 1997	P: aerobic training. walking. I: low, very light (9)-somewhat hard (13) according to Borg RPE scale. F/D: 3 mnths, 3x/wk, ? min. O/S: individual exercise, NA. vs. home assignments.	AT: ? C: ?
Kramer, 1999	P: aerobic training. Walking. I: ? F/D: 6 mnths,?,? O/S: ?, ? vs. flexibility training. anaerobic stretching and toning exercise.	AT: ? FT: ?
Lachman, 2006	P: strength training. 35 min videotaped program of 10 exercises using elastic bands. 10 min warm-up; 25 min resistance exercises; 5 min cool-down. I: using bands with higher resistance when > 10 repetitions possible without significant fatigue. F/D: 26 wks, 3 x/wk, 35 min. O/S: individual at home, 2 visits by physical therapist or trainer. vs. waiting list control group.	ST: 93 (38)%, range 0-218% of 78 required sessions. NIC: NA
Madden, 1989[b]	P: aerobic training. 10 min warm-up; 30 min bicycle ergometry + 15 min brisk walking or jogging with supplemented arm ergometry for 5 min; 5 min cool-down. I: 70% HRR. F/D: 16 wks, 3x/wk, 60 min. O/S: group-based, ? vs. non aerobic yoga training: 16 wks, 2x/wk, 60 min. vs. waiting list control group.	AT: 90% Yoga: 90% NIC: NA
McMurdo, 1994[a]	P: strength + flexibility training. 10 min warm-up; 25 min seated isometric exercise; 10 min cool-down. I: increasing number of repetitions. F/D: 6 mnths, 2x/wk, 45 min. O/S: group-based, physiotherapist. vs. reminiscence therapy.	SFT: 72%, range 18-98% C: 62%, range 29-100%
McMurdo, 2000[a]	P: strength + flexibility + balance training. seated exercise on music. I: increasing number repetitions, longer muscle contractions. F/D: 6 mnths, 2x/wk, 30 min. O/S: group-based, ? vs. reminiscence therapy.	SFBT: 81%, range 33-100 C: 89%, range 35-100
Molloy, 1988	P: strength + balance training. I: low. F/D: 3 mnths, 3x/wk, 10-35 min. O/S: group-based, physiotherapist. vs. non-intervention control group.	SBT: 71%, range 31-94 C: NA
Moul, 1995	P: aerobic training. Walking. I: 60% HRR, after 8 weeks 65%. F/D: 16 wks, 5x/wk, 30-40 min. O/S: group-based, exercise leader. vs. strength training. I: progressive resistance using weights. vs. flexibility training I: low.	AT: ? ST: ? FT: ?

Oken, 2006	P: aerobic training. walking outdoors on 400-m track. I: level 6-7 perceived exertion scale, 70% of Hrmax. F/D: 6 mnths, 1x/wk, 60 min + encouraged to exercise individually ≥ 5x/wk. O/S: group-based, personal trainer. vs. Iyengar yoga. 7-8 poses were taught per week to a total of 18 standing and seated poses, each pose held for 20-30 sec, rest between poses 30-60 sec, emphasis on breathing for relaxation; session ending with 10 min deep relaxation in supine position using progressive relaxation, visualisation + meditation. I: low. F/D: 6 mnths, 1x/wk, 90 min + daily home practice encouraged. O/S: group based, Iyengar trained teacher. vs. waiting list control group.	AT: 69 (19)% Yoga: 78 (20)% NIC: NA
Okumiya, 1996	P: aerobic + strength + flexibility training. 5 min warm-up; 50 min aerobic exercise (low intensity aerobic exercise e.g. walking, dodge ball; callisthenics e.g. stretching and ROM exercise; exercises aimed at neuromotor coordination; muscle strengthening exercises for extremities, abdominal wall, back); 5 min cool-down. I: low. F/D: 6 mnths, 2x/wk, 60 min. O/S: group-based, physical educator, medical doctor, 5 nurses. vs. non intervention control group.	ASFT: 86%, range 59-100 NIC: NA
Perrig Chiello, 1998	P: strength training. 10 min warm-up; 8 resistance exercises on machines: leg press, bench press, leg curls, seated row, leg extension, preacher curls, trunk curls, back extension. I: ? F/D: 8 wks, 1x/wk, ? min. O/S: ?,? vs. waiting list control group.	ST: ? NIC: ?
Scherder, 2005[a]	P: aerobic training. self paced slow walking with aid. I: low. F/D: 6 wks, 3x/wk, 30 min. O/S: ?,? vs. flexibility training. hand-face exercise. hand exercise= bending and stretching fingers + sliding wooden club by moving fingers. facial activity= producing 7 facial expression used with rehabilitation after paralysis of the facial nerve. I: low. F/D: 6 wks, 3x/wk, 15 min. O/S: ?,? vs. control: half social visits, half no intervention.	AT: ? FT: ? C: ?
Stevens, 2006[a]	P: aerobic training. gentle aerobic exertion moving joints and muscles (on music). I: ? F/D: 12 wk, 3x/wk, 30 min. O/S: group-based, researchers. vs. social visits. vs. non intervention control group.	AT: ?/ C: ?/ NIC: ? only subjects attending ≥ 75% of AT or C sessions included
Stevenson, 1990	P: aerobic + flexibility training. 15 min warm-up (stretching + callisthenics); 30 min stationary cycle ergometry; 15 min cool-down (slow walking and stretching). I: moderate intensity, 60-70% HRR. F/D: 9 mnths, 3x/wk, 60 min. O/S: group-based, exercise session leaders. vs. same program, but low intensity, 30-40% HRR.	AFT: ? AFTlow: ? only subjects attending ≥ 70% of sessions included
Tsutsumi, 1997	P: strength training. 12 resistance exercises on machines: leg extension, leg curl, shoulder press, bench press, lateral pull-down, fly, triceps, press-down, arm curl, back extension, seated row, abdominal flexion. I: high: 2 sets of 8-10 reps at 75-85% of estimated repetition maximum. Increasing during the programs. F/D: 12 wks, 3x/wk, ? min. O/S: group-based, ? vs. same program, but low intensity. I: 2 sets of at 55-65% of 1 repetition maximum. vs. non intervention control group.	ST: nearly 100% STlow: nearly 100% NIC: NA
van de Winckel, 2004[a]	P: strength + flexibility + balance training. seated dance. I: ? F/D: 12 wks, 1x wk/ 30 min. O/S: group-based, physiotherapist. vs. individual daily conversation with physiotherapist.	SFBT: ? C: ?
Williams, 1997	P: aerobic + strength + flexibility + balance training. 5 min warm-up; 35 min conditioning (predominantly aerobic exercise); 15 min stretching seated on floor or chair; 5-10 min cool-down. I: emphasis on social interaction and enjoyment, no measures of intensity. F/D: 42 wks, 2x/wk, 60 min. O/S: group-based, trained exercise leaders. vs. non intervention control group.	ASFBT: 72% in those who completed program (n= 71), range 32-100% NIC: NA

A= Aerobic; S= Strength; F= Flexibility; B= Balance; T= Training; C= Control; NIC= Non-Intervention Control; Hrmax= Maximum Heart Rate; HRR= Heart Rate Reserve; low= Low intensity; MET= Metabolic Equivalents; NA= Not Applicable; no= Number; ROM= Range of Motion; reps= Repetitions; RPE= Rating of Perceived Exertion; [a] Study among subjects with cognitive decline; [b] Cross-over design (only data before cross-over considered); [c] Unless stated otherwise, frequency + duration, organisation and supervision of the comparison interventions match these characteristics of the exercise interventions

TABLE 5: Description of neuropsychological outcome measures, domains of cognition, and between group differences

Author, year	Outcome measures	Cognitive domain as reported by authors	n randomised (R)/ n analysed (A)	Between group differences (exercise vs. control)
Baum, 2003[a,b]	1. MMSE	-	R: 20 (11SFT/ 9NIC) A: idem	3.1 points, ES (90% CI)= 0.5 (0.12; 0.95), p= 0.02
Blumenthal, 1991[b]	1. short memory (Randt memory test) 2. digit span (WAIS-R) 3. Benton revised visual retention test 4. selective reminding test 5. digit symbol subtest (WAIS-R) 6. trail making test 7. 2 & 7 test 8. nonverbal fluency test 9. verbal fluency test 10. Stroop colour word test	1-4: memory 5-7: perceptual motor function 8-10: miscellaneous	R: 101 (33AT/ 34yoga/ 34NIC) A: 97 (31AT/ 34yoga/ 34NIC)	-
Emery, 1990	1. digit symbol (WAIS-R) 2. digit span (WAIS-R) 3. writing digits 4. writing words	1-4: fluid intelligence, i.e. problem solving, integration new information	R: 48 (15ASFT/ 15C/ 18NIC) A: 39 (14ASFT/ 25C+NIC)	-
Fabre, 2002	1. recall, learning, orientation, manipulation, mental problems, verbal fluency, denomination, visual reproduction (BEC 96 questionnaire) 2. orientation, mental control, immediate recall, digit span, reverse digit span, visual reproduction, paired associates learning (WMS)	1. cognitive problems, i.e. praxi, nosi, language 2. mnesic deterioration	R: 32 (8AT/ 8C/ 8AT+C/ 8C) A: idem	-
Hassmen, 1997	1. immediate (1 trial)/ delayed recall: 16 one-syllabus words 2. face recognition: 18 faces + 18 distracter faces 3. simple reaction time task 4. choice reaction time task 5. digit span test: starting with 3 digits, longest series after 10 minutes	1-2: memory	R: 40 (20AT/ 20C) A: ?	- better face recognition task in men, $p < 0.04$ - better digit span test in women, $p < 0.001$
Kramer, 1999	1. task switching: measure of cost of switching between tasks 2. response compatibility: measure of ability to ignore task irrelevant stimuli 3. stopping: measure of the ability to abort pre-programmed action	1-3: executive control processes	R: 124 (?AT/ ?FT) A: idem	better performance parts of the 3 tests depending on executive control processes
Lachman, 2006	1. reverse digit span (WAIS)	working memory span	R: 210 (102ST/ 108NIC) A: ?	-

Madden, 1989[b]	1. letter search: compare a visually presented probe letter with a set of letters held in memory composed of 2,4, or 6 different letters (Sternberg task, 90 min) 2. word comparison: deciding whether 2 words are synonyms (90 min)	1. working memory 2. retrieval from long-term memory	R: 85 (28AT/ 30yoga/ 27NIC) A: 79 (25AT/ 28yoga/ 26NIC)	-
McMurdo, 1994[a]	1. MMSE 2. speed of response to visual stimulus (recognition movement time + time taken to respond to the stimulus)	1. cognitive state 2. choice reaction time	R:65 (36SFT / 29C) A: 55 (32SFT/ 23C)	less decline on MMSE, p= 0.06
McMurdo, 2000[a]	1. MMSE 2. reaction time	-	R: 133 (77SFBT/ 56C) A: 90 (52SFBT/ 38C)	-
Molloy, 1988	1. total recall (4 trials), immediate free recall (trial 1), recognition test with 3 distraction slides (7 colour slides test) 2. digit symbol (WAIS) 3. forward + reverse digit span (WAIS) 4. logical memory (WMS) 5. word fluency test (Western Aphasia Battery) 6. MMSE	1. memory, language, visual perception 3. short-term memory 5. motivation, attention, concentration, retrieval from long-term memory	R: 50 (25SBT/ 25NIC) A: 45 (23SBT/ 22NIC)	less decline in word fluency test, $p < 0.025$
Moul, 1995	1. immediate memory, recent memory, temporal orientation, problem solving and abstract reasoning, organisation, auditory processing (Ross Information Processing Assessment)	information processing abilities	R: 30 (10AT/ 10ST/ 10FT) A: ?	better 'organisation' and 'auditory processing' in AT vs. ST and FT, $p < 0.5$
Oken, 2006	1. Stroop colour word test 2. 10 word learning test 3. letter number sequencing (WAIS) 4. spatial attention task 5. simple reaction time 6. choice reaction time	1. attention 2-3: working memory 4. shifting spatial attention	R: 135 (47AT/ 44yoga/ 44NIC) A: 118 (38AT/ 38yoga/ 42NIC)	-
Okumiya, 1996	1. MMSE 2. Hasegawa dementia scale revised 3. visuospatial cognitive performance test: eye-tracking performance vigilance task	1-2: overall cognition 3: concentration, non verbal visuospatial orientation, reaction time	R: 42 (21ASFT/ 21NIC) A: idem	-
Perrig Chiello, 1998	1. digit symbol test (WAIS) 2. immediate/ delayed recall + free recall: 8 two-syllabi words 3. immediate/ delayed recall: 8 distracter words	1: visuomotor coordination, attention, information processing speed. 2-3: memory	R: 46 (23ST/ 23NIC) A: idem	- better immediate + delayed recognition, p= 0.07 and p= 0.08

TABLE 5: Continued

Author, year	Outcome measures	Cognitive domain as reported by authors	n randomised (R)/ n analysed (A)	Between group differences (exercise vs. control)
Scherder, 2005[a]	1. category naming: 1 min animals, 1 min professions 2. trail making A + B 3. digit span (WMS-R) 4. visual memory span (WMS-R) 5. immediate/ delayed recall + recognition (CVLT) 6. face recognition (RBMT) 7. picture recognition (RBMT)	1-2: executive functions 3-7: memory	R: 43 (15 AT/ 13 FT/ 15 C) A: ?	- better category naming in walk vs. control (ES 0.16; p= 0.02) + HF vs. control (ES 0.12; p= 0.04) - better trail making in walk vs. control (ES 0.10, p= 0.07) and HF vs. control (ES 0.19, p= 0.02)
Stevens, 2006[a]	1. clock drawing test	progression symptoms dementia	R: N= 120 (?/ ?/ ?) A: N=75 (24AT/ 21C/ 30NIC)	less decline in AT vs. C, p= 0.002
Stevenson, 1990	1. visual reproduction, digit span, verbal memory, verbal pairs test (mental status test (Strub and Black), based on WMS)	attention/concentration, orientation, short term memory, higher cognitive functioning	R: 97 A: 72 (39AFT/ 33AFTlow)	-
Tsutsumi, 1997	1. mental arithmetic task: counting back with 7 from 3-digit number for 2 min 2. mirror drawing task: move cursor along track using a mouse that has to be moved in opposite direction	-	R: 42 (14ST/ 14STlow/ 14NIC) A: 41 (13ST/ 14STlow/ 14NIC)	-
van de Winckel, 2004[a]	1. MMSE 2. short-term memory, orientation, visuoconstructional problems, category fluency, copying figures, free recall 8 words (Amsterdam Dementia Screening test 6)	-	R: 25 (15SFBT/ 10C) A: 24 (15SFBT/ 9C)	- improved MMSE, ES= 0.5, p= 0.02 - improved fluency, p= 0.01
Williams, 1997	1. digit span subtest (WAIS-R) 2. picture arrangement subtest (WAIS-R) 3. Cattell's matrices	1-3: memory + fluid intelligence	R: 187 (94ASFBT/ 93NIC) A: 149 (71ASFBT/ 78NIC)	- improved digit span, p= 0.004

A= Aerobic; S= Strength; F= Flexibility; B= Balance; T= Training; C= Control; NIC= Non-Intervention Control; CVLT= California Verbal Learning Test (or modification in another language); ES= effect size; low= Low intensity; RBMT= Rivermead Behavioral Recognition Test; WAIS-(R)= Wechsler Adult Intelligence Scale (Revised); WMS-(R)= Wechsler Memory Scale (Revised); [a] Study among subjects with cognitive decline; [b] Cross-over design (only data before cross-over considered)

DISCUSSION

Twenty-one randomised controlled trials on the effect of physical exercise on cognition were included in this systematic review and summarised with respect to characteristics of the exercise programs and examined cognitive domains. Fifteen trials were performed among cognitively healthy subjects and six among subjects with cognitive decline. Inconclusive evidence was found for the effect of exercise programs on cognition. Twelve studies, including two in subjects with cognitive decline, found no significant effect of exercise on cognition. Nine studies, including four among subjects with cognitive decline, did observe a beneficial effect of aerobic or strength training on at least one measure of cognition. Observed improvements comprised information processing, executive functions and memory in cognitively healthy adults and global cognitive function and executive functions in adults with cognitive decline. Unfortunately, because of the diversity in exercise programs, measures of cognition, and study populations in included studies, it is impossible to draw valid conclusions about which type of exercise program is most effective, for what aspect of cognition and for which specific population. Moreover, overall quality of the included studies was poor. Only five of the 21 studies were qualified as high quality studies.

It is striking that beneficial effects were observed in the majority of studies, i.e. four out of six, performed among adults with cognitive decline. Moreover, in one other study, between-group differences on global cognitive function nearly reached significance ($p= 0.06$).[28] In contrast, in one third of the studies in cognitively healthy adults, i.e. five out of 15, beneficial effects were observed. One study observed a nearly significant effect of strength training on memory compared with a non intervention control group ($p= 0.07$).[34] Etnier et al. found that the intervention effect decreased with increasing methodological quality.[5] However, in the present review, mean quality score of the studies among elderly with cognitive decline was higher than the mean quality score of studies in cognitively healthy elderly (4.3 versus 3.1 respectively). Both mean scores did not reach the cut-off point of five points which was used to indicate high-quality. Also, because the number of studies in subjects with cognitive decline was relatively small, the differences in the proportion of studies finding beneficial effects may be coincidentally.

In the present review, studies on both aerobic and strength training programs were included. With respect to the exercise programs, it must be noted that programs were qualified as aerobic or strength training by the authors of this review, also if intensity was not reported or reported to be low. The possibility exists that some of these programs were aimed at the maintenance of aerobic fitness and strength, rather than at improvement thereof.

The finding that beneficial effects of exercise on cognition are observed in both subjects with and without cognitive decline is very relevant. This review shows that regular exercise can be of benefit irrespective of cognitive status. This is in line with previous reviews.[4-8] Inevitably, some overlap exists between studies included in the present review and in previous reviews. However, the present study is current up to February 2007. Furthermore, it differs from previous papers since only RCT's were included and the effect of different exercise programs was compared between cognitively healthy elderly and elderly with cognitive decline. In contrast, previous reviews and meta-analyses included only cognitively healthy subjects[4-6] or subjects with cognitive decline[7,8]; included all intervention studies irrespective of design[5,6,8,9]; did not perform a standardised quality assessment[4,6,8,9]; included specific exercise programs with an aerobic training component only[4]; applied a very broad definition of exercise training also including recreational therapy[7]; or focused on cardiovascular risk factors.[8]

In the literature, ample attention has been paid to the pathways by which improved aerobic fitness may benefit cognition. In a recent exercise intervention study, increased function of particular sections of the brain was observed in subjects participating in aerobic fitness training, compared with subjects participating in non-aerobic flexibility training.[41] Moreover, in a meta-analysis on the effect of aerobic exercise on cognition in the elderly it was concluded that aerobic training induced beneficial effects on executive control.[4] However, a larger effect was observed of aerobic training in combination with strength training. Etnier et al. (2006) [42] examined the association between aerobic fitness and cognition using meta-regression techniques and concluded that the pathway of improved aerobic fitness resulting in better cognition was not supported by intervention studies. Etnier et al. recommended to also address other physiological and psychological variables that may mediate the relation between exercise and cognition.[42] Literature on the pathways by which strength training may influence cognition is barely available. The possibility exists that strength training improves the conditions to participate in aerobic training. Especially in older adults, improved muscle strength of major muscle groups, such as the quadriceps, may result in better ability to participate in aerobic exercise programs. Considering its importance and complexity, the study of potential pathways by which exercise benefits cognition will remain in the centre of interest in future studies.

Limitations

In general, publication bias endangers the external validity of reviews and meta-analyses. In the present review, in half of the studies evidence was found for a beneficial effect of exercise on cognition and in the other half there was not. Also in the present review, publication bias cannot be excluded.

Even though a standardised Delphi-list was used to assess methodological quality, subjective interpretation of the authors on how to score Delphi items may have occurred, since no specific scoring rules are provided.[17] In order to minimise this, some rules were set by the authors, e.g. scoring 'unclear' for 'specified eligibility criteria' if only exclusion criteria are reported, scoring 'no' for 'blinding of subjects' if the study included a non-intervention control group. Furthermore, methodological aspects of included studies were assessed by two authors independently.

Anyhow, the poor methodological quality and the predominantly small sample sizes of the included studies are the most important limitations of the present review. Especially treatment allocation and blinding of subjects and exercise trainers was not well described. The lower the quality, the higher the liability that study results are biased by threats to internal and external validity. Moreover, in thirteen studies data were analysed using (M)ANOVA. It is important to use more sophisticated statistical techniques that provide better insight into the direction and precision of between group differences. Furthermore, intention-to-treat analysis provides optimal information about the effectiveness of an intervention, since data of all randomised subjects are included in the analysis. In the present review, only half of the included studies performed an intention-to-treat analysis. The possibility exists that actual methodological quality of the studies was underestimated because of inappropriate reporting. Therefore, it is urgently advised to comply with the CONSORT statement guidelines for the standardised reporting of RCT's.[43] In trials on exercise interventions, additional attention should be paid to the reporting of concealment of treatment allocation and blinding of subjects and exercise trainers.

The determination of study populations with and without cognitive decline on the basis of mean MMSE scores may be considered arbitrary. However, this was the most feasible method to discriminate between groups on the basis of available information in the included studies. The applied cut-off point of 24 is commonly used to distinguish subjects with and without cognitive decline for research purposes, but in reality the distinction is not that clear. To illustrate this, the study population in which the mean MMSE was 25 was qualified as cognitively healthy.[30] However, considering the standard deviation of five

points, this study probably included subjects with cognitive decline. Allocating the study of Molloy et al. (1988) to the group of subjects with cognitive decline adds evidence to the effectiveness of exercise on cognition, since subjects in the strength training group showed less decline in word fluency, which is a measure of executive functions, compared with a non-intervention control group. In future exercise intervention studies, a description of the cognitive status of included subjects should be provided in order to provide useful information for reviews, meta-analyses and practice.

Finally, the classification of neuropsychological tests according to neuropsychological focus is disputable, since cognitive functions are interwoven and neuropsychological tests in general do not measure a single aspect of cognition.[44] In the results section, tests were categorised into cognitive domains as reported by the authors of the included studies. Since cognitive decline is associated with a decline in memory, it is striking that no effect of exercise on memory was found in studies among subjects with cognitive decline. This also is in contrast to a previous review, including intervention studies irrespective of design, in which a beneficial effect of exercise on memory was observed among elderly with dementia.[8] A logical explanation may be that memory was not assessed in RCT's among subjects with cognitive decline included in the present review. Indeed, memory was only extensively assessed in one of the studies in elderly with cognitive decline.[35] In that study no effects on these tests were observed. One study[39], only included a measure of short-term memory. In four studies, the MMSE was assessed, which does include a measure of immediate recall of three words in which the presence of a ceiling effect is likely. Moreover, three word recall alone is a very insensitive measure of memory, which is probably not responsive to change. Therefore, future studies among subjects with cognitive decline should include a more thorough assessment of memory using neuropsychological tests that are responsive to change.

In conclusion, the present review addressed the difference in effects of exercise programs on cognition between subjects with and without cognitive decline. Since half of the studies observed some beneficial effects of both aerobic and strength training, predominantly on executive functions, the conclusion seems justified that exercise is beneficial to a certain extent in both cognitively healthy adults and adults with cognitive decline. Unfortunately, the methodological quality of the included studies was poor. More studies of a methodological high quality are needed in order to gain better insight into the effect of exercise programs on cognition in populations with different cognitive status. Furthermore, since the number of included studies was insufficient to draw conclusions about the specific characteristics of potentially effective programs in terms of content, intensity, and duration, these issues should also be addressed in future research.

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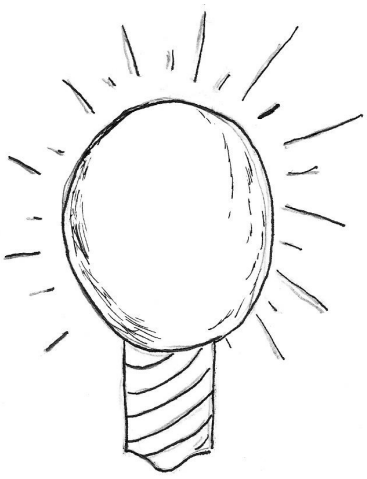
Protocol for Project FACT: a randomised controlled trial on the effect of a walking program and vitamin B supplementation on the rate of cognitive decline and quality of life in older adults with mild cognitive impairment [ISRCTN19227688]



JGZ van Uffelen, M Hopman-Rock, MJM Chin A Paw, W van Mechelen
BMC Geriatrics 2005;5:18

ABSTRACT

Background

Since the number of older adults is growing considerably, the prevalence of individuals with cognitive decline is increasing. The literature provides promising results on the beneficial effects of physical exercise and vitamin B supplementation on cognitive function both in cognitively healthy, as well as in demented older adults.

Design and methods

The design is a two-by-two factorial randomised controlled trial. The study population consists of community-dwelling elderly people, between 70 and 80 years, with mild cognitive impairment (MCI). In the RCT, the effect of two interventions, a walking program and vitamin B supplementation, is examined. The walking program (WP) is a group-based program designed to improve aerobic fitness; frequency two sessions per week; session duration one hour; program duration one year. Non-walking groups participate in a placebo activity program (PAP): low intensity non-aerobic group exercises, like stretching, with the same frequency, session and program duration. Vitamin supplementation consists of a single daily vitamin supplement containing 5 mg folic acid, 0,4 mg vitamin B12 and 50 mg vitamin B6, for one year. Participants not receiving vitamin supplements are daily taking an identically looking placebo pill, also for a year. Participants are randomised to four groups: 1) WP and vitamin supplements; 2) WP and placebo supplements; 3) PAP and vitamin supplements; and 4) PAP and placebo supplements. Primary outcome measure is cognition. Secondary outcome measures include quality of life, aerobic fitness and physical activity levels, and homocysteine and vitamin B concentrations.

Discussion

No large intervention study has been conducted yet on the effect of physical exercise and vitamin supplementation in a population-based sample of elderly people with MCI. The objective of the present paper is to describe the design of a randomised controlled trial examining the effect of a walking program and vitamin B supplementation on the rate of cognitive decline in older adults with MCI.

Trial Registration

International Standard Randomised Controlled Trial Number Register, 19227688, http://www.controlled-trials.com/isrctn/.

INTRODUCTION

Because cognitive function decreases with age, and the number of older adults is increasing worldwide, the number of older adults with cognitive dysfunction is also increasing. Since no cure for dementia is available yet, this process will put a considerable burden on the healthcare system and on society in general. Therefore, for both individuals and society, it is necessary to develop strategies for maintaining physical, mental and cognitive wellbeing of the ageing population.

This paper describes the design of a randomised controlled trial on the effect of a moderate intensity walking program and vitamin B supplementation in an older population with mild cognitive impairment (MCI) recruited from the general population.

Mild cognitive impairment

MCI refers to a stage in which persons experience memory loss to a greater extent than is expected for age, but do not yet meet currently accepted criteria for clinically probable dementia or Alzheimer disease (AD).[1] Prevalence of MCI in older adults with a mean age of 75 years is three to four percent.[2,3] Compared with elderly people with normal cognitive function, adults with MCI have an increased risk to develop dementia or AD.[1,4,5] Progression rates to dementia and AD for adults with MCI vary from six percent to 25 percent per year, depending on the criteria for MCI.[6] The rate of progression to AD in adults with MCI according to the criteria of Petersen et al. is 12 percent, compared with a rate of one to two percent per year in control subjects.[4]

As the stage of MCI may be the optimum stage at which to intervene with preventive therapies[7,8], new treatments to prevent development of AD are targeting older adults with MCI.[7]

Physical exercise

The hypothesis of physical exercise positively influencing cognition is supported by observational studies that found that higher physical activity levels were associated with a reduced risk of cognitive decline and dementia in healthy elderly people.[9-13] Positive effects of exercise programs on cognitive function have been found also in various trials among cognitively healthy elderly people.[14-17] Programs lasted from two months[14] to one year[16], frequency and intensity differed per program. Improvements in memory[14], immediate recall[16,17] and tasks requiring executive control processes[15] have been reported. Also a number of reviews and a meta-analysis have been conducted on the effects of physical

exercise on cognition in healthy older adults.[18-20] Exercise seems to have a positive effect on cognitive functioning, but findings in the individual studies are contradictory and the effect size can be considered small. However, two recently published meta-analyses reported moderate effect size values, around 0.5, from group based aerobic fitness training on cognitive performance in healthy elderly people[21] and from various types of exercise programs in elderly with dementia.[22]

Besides an effect on cognitive function, Biddle and Faulkner[23] concluded in their review that clear beneficial effects from physical activity are evident for quality of life in older adults.

Possible pathways for the effect of physical activity on cognitive function are increased blood flow to the brain, improved vascularisation, improved neurogenesis, increased neurotransmitter availability and better neural efficiency.[24,25]

Vitamin B supplementation

Cognitive function may benefit as well from supplementation with folic acid, vitamin B12 and vitamin B6 (FA/B12/B6 respectively). Metabolic deficiencies of these vitamins are relatively common in older adults[26,27], even in the presence of normal serum vitamin concentrations.[28] Low concentrations of FA/B12/B6 seem to be associated with poorer cognitive function.[29-31] Besides a reverse effect on cognitive function, FA/B12/B6 deficiencies result in increased concentrations of the amino acid homocysteine[32], as these vitamins are linked to the metabolism of homocysteine. An increased homocysteine concentration has been found to be a strong independent risk factor for the development of dementia and AD as well.[33] Negative associations have been found between increased homocysteine concentrations and global cognitive performance[34-36], memory[37,38], psychomotor speed[38,39] and spatial copying skills[29], even in the generally accepted normal range of homocysteine (25th; 75th percentile= 7.6; 11.3 micromol/liter).[38] Above a threshold of approximately 14 micromol/liter significantly lower cognitive performances were observed as well.[39-41]

Supplementation with vitamin B reduces the homocysteine concentration.[42,43] Supplementation with folic acid after standardisation for pre-treatment blood concentrations of homocysteine and folic acid resulted in an approximate decrease of homocysteine concentration of 25 percent. Vitamin B12 produced an additional seven percent reduction.[44] Few experimental studies have been conducted on the effect of vitamin B supplementation on cognitive performance in older adults. Bryan and Calvaresi (2002)[45] found a significant effect on memory performance after 35 days of

supplementation with folic acid, vitamins B12 and B6 in healthy middle aged and older women. Fioravanti et al.[46] concluded in a double blind controlled trial that 15 mg folic acid daily for 60 days given to older adults with global impairment in all components of memory functioning (i.e. a more seriously decline than MCI), appeared to improve their memory. Vitamin B12 injections of different doses improved memory in older adults with B12 deficiency and without cognitive impairment in a single blind controlled trial.[47] Finally, cognitive performance in adults with increased plasma homocysteine concentrations and a diagnosis of mild to moderate dementia improved after combined supplementation of 5 mg folic acid and 1 mg vitamin B12 daily for two months.[48] Unfortunately most of these trials included few subjects and, therefore, results have to be interpreted with care.

Calvaresi and Bryan (2001) hypothesised that FA/B12/B6 supplementation may affect cognitive performance via two interrelated ways: a direct and possibly acute influence via hypomethylation and a longer term influence on homocysteine concentrations resulting in structural vascular changes in the brain.[49]

No clinical trials are available yet that have examined the effect of physical exercise and vitamin supplementation in a population-based sample of adults with MCI. Therefore, the main objective of Project FACT (Folate physical Activity Cognition Trial) is to examine the effect of a walking program and vitamin B supplementation on the rate of cognitive decline in adults aged 70 to 80 years with mild cognitive impairment in a randomised controlled trial. Also, effects of both interventions on quality of life, aerobic fitness and habitual physical activity levels, and homocysteine and vitamin B concentrations will be examined.

METHODS

Study design

The study is designed as a randomised, placebo controlled intervention trial, based on a two-by-two factorial design. The design is presented in Figure 1. It is assumed that the effect of both interventions is independent. The study protocol was approved by the VU University Medical Center medical ethics committee.

Setting

This study is carried out in Alkmaar, a medium sized city in The Netherlands, with approximately 100,000 inhabitants.

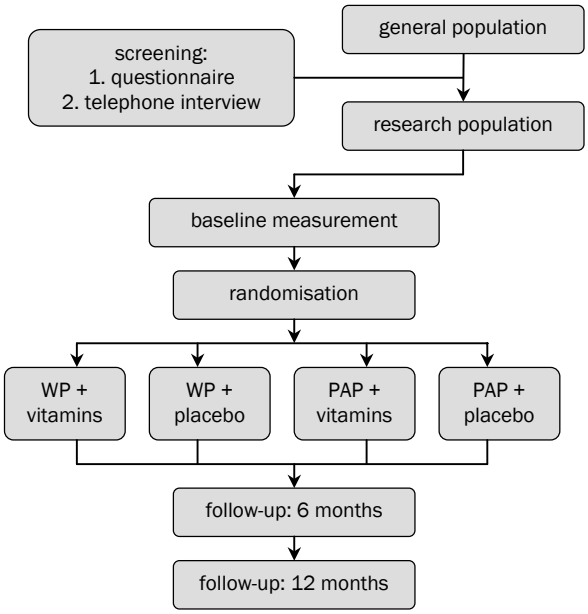


FIGURE 1: Design

WP= Walking Program; PAP= Placebo Activity Program

Study population

This study is targeted at a population-based sample meeting the five criteria for mild cognitive impairment: i.e. memory complaint, memory impairment, normal general cognitive function, normal activities of daily living and not demented.[4] In the recruitment procedure, the criteria for MCI are checked in both a questionnaire and a telephone interview. Other inclusion criteria for participating in the trial are checked for only in the questionnaire (Table 1).

Questionnaire

To recruit participants, a questionnaire is sent to all independently living elderly people in Alkmaar, with an age between 70 and 80 years old. Their addresses are provided by the register of population of the municipality of Alkmaar. Primary aim of the questionnaire is to check two criteria for MCI, memory complaints and normal activities of daily living. Memory complaints are assessed by the question 'do you have memory complaints' and the cognition scale of Strawbridge.[50] Activities of daily living (ADL) are assessed using the Groningen Activity Restriction Scale (GARS).[51] Secondary aims are to collect demographic variables and to check the other inclusion criteria for trial participation. Together with filling in the questionnaire, participants are requested to give informed consent.

TABLE 1: Inclusion criteria

Criteria for Mild Cognitive Impairment (1-4) and other inclusion criteria for the RCT (5-11)
1. Self reported memory complaints (answer 'yes' to question 'do you have memory complaints', or at least twice 'sometimes' at cognition scale of Strawbridge)
2. No report of disability in activities of daily living on GARS-scale, except on the item 'taking care of feet and toe nails'
3. Objective memory impairment; 10 WLT delayed recall ≤ 5 + percentage savings ≤ 100
4. Normal general cognitive functioning/ absence of dementia; TICS ≥ 19
5. Being able to participate in moderate intensity physical activity without making use of walking devices, e.g. rollator or walking frame
6. Not using vitamin supplements/ vitamin injections/ drinks with dose of folic acid, vitamins B12 or B6 comparable to vitamin supplement given in intervention
7. Not suffering from epilepsy, multiple sclerosis, Parkinson's disease, kidney disorder requiring haemodialysis, psychiatric impairment
8. Not suffering from depression as measured by the GDS (cut off ≤ 5)
9. Not using medication for rheumatoid arthritis or psoriasis interfering with vitamin supplement
10. No alcohol abuse (men < 21 consumptions a week, women < 15 consumptions a week)
11. Not currently living in or on a waiting list for a nursing home

RCT= Randomised Controlled Trial; GARS= Groningen Activity Restriction Scale; WLT= Word Learning Test; TICS= Telephone Interview for Cognitive Status; GDS= Geriatric Depression Scale

Telephone interview

Respondents fulfilling the inclusion criteria are requested to participate in a telephone interview for cognitive status. In this telephone interview, a brief measure of general cognitive function (TICS)[52] and a modified version of the ten word learning test[53] are administered. Adults with a score of 20 or more on the TICS, corresponding to normal cognitive function, and with a score of five or less on the delayed recall task of the ten word learning test, are considered to have mild cognitive impairment. A delayed recall score of five or less corresponds with one standard deviation below normal performance.[54] Participants fulfilling these criteria receive an invitation letter for a baseline measurement during a personal interview.

Sample size

The aim is to enrol 170 participants. A power analysis has been executed on the auditory verbal learning test. To be able to detect a difference of 5 points on immediate recall, 34 participants per group are required, and thus 136 participants in total. These numbers are based on a power of 80 percent and a significance level of 0.05. We expect a drop-out rate of 25 percent, based on experiences with comparable research. Therefore, 170 participants will be recruited.

Randomisation

To ensure an equal distribution of physically inactive and active participants in each group, participants are classified as active or inactive on the basis of their activity level as measured using the LASA physical activity questionnaire.[55] Adults with an activity level exceeding the median level of the whole group are classified as active and adults below this level are classified as inactive. Active and inactive participants are allocated separately and randomly to one of the four intervention groups using the option 'random sample of cases' in the statistical computer program SPSS.

Blinding

The study is conducted double blind. The key of coding for FA/B12/B6 supplementation is only known to the manufacturer of the supplements, who will decode the key after data analysis. All outcome measures on cognition and quality of life are assessed by independent examiners unaware of group allocation.

Co-interventions and compliance

Co-interventions during the intervention period are discouraged by asking adults not to start an exercise program or vitamin supplementation while being a participant. Both vitamin supplementation and physical activity level will be asked for at baseline and after six and 12 months. Adherence to the exercise programs is assessed as the percentage of attended sessions. Compliance with the vitamin supplementation is verified by pill counts and determining blood vitamin concentrations.

Interventions

Walking program (WP)

The walking program is based on 'Sportive Walking', an existing aerobic exercise program.[56] Each session consists of a warm-up, moderate intensity walking exercises and a cool-down. Sessions for Project FACT are developed by two certified walking instructors and recorded in a manual. The duration and intensity of the WP are increased gradually during the program by increasing the total walking time and distance. The WP is developed in such a way that all participants can perform the walking exercises at their own level, but still walk in a group. This is for example established by using walking routes with the same beginning and end. Sessions take place outdoors in municipal parks in Alkmaar. Only when it is slippery due to snow or freezing rain, the session will be cancelled.

Placebo activity program (PAP)

The PAP is developed by four experienced exercise instructors. The program consists of an introduction, low intensity non-aerobic group exercises such as light range of motion movements and stretching, and a closing. Sessions are divided into five themes: relaxation, activities of daily living, balance, flexibility, posture, and a combination of all. For each theme three sessions are developed and the entire series of 18 sessions is repeated during the intervention period. The program takes place in a community center.

Both programs are group-based and last one year, the frequency is twice a week and session duration is 60 minutes. The intensity is checked by heart rate monitors (Polar, Vantage NV) and Borg scales in a sub sample of the population during one session at baseline and after twelve months and during two sessions at six months follow up.

To provide an intervention class in or near the participants' own neighbourhood, eight classes for the walking program and eight classes for the placebo activity program are started in four districts. These classes are organised especially for the study and only study participants are able to join. All exercise classes are supervised by qualified instructors. In total four trained walking instructors for the walking program, and four exercise instructors for the placebo activity program are hired for the study. The number of participants in a group is 19 at the most.

Vitamin B supplementation

Participants in the intervention group are asked to take daily one pill containing 5 mg folic acid, 0.4 mg vitamin B12 and 50 mg B6 during a year. Participants who do not get FA/B12/B6 supplementation receive identically looking placebo pills. The pills are packed in blister packs containing seven pills that are labelled for each day of the week.

Measurements

All outcome measures are collected at baseline, and after six and 12 months intervention. The primary outcome measures are measures of cognitive function. Secondary outcome measures are measures of quality of life, aerobic fitness and habitual physical activity levels, and homocysteine and vitamin B concentrations. Also, physical measures are performed. Most data on cognition and quality of life are gathered during a standardised interview. These face-to-face interviews are conducted in the Medical Center Alkmaar and last at maximum 90 minutes, including a short break.

Primary outcome measures

Five interviewer administered cognitive outcome measures are chosen to assess different aspects of cognition. Only the informant questionnaire is self administered.

- Mini Mental State Examination (MMSE) [57]: general cognitive function is measured with the MMSE. The MMSE consists of 11 questions concerning orientation, registration, attention and calculation, recall and language. The maximum score is 30 and a score below 24 is considered abnormal for dementia screening.

- Auditory Verbal Learning Test (AVLT) [58]***:*** a Dutch version of the AVLT is used. This is a measure of memory in which immediate and delayed recall are assessed. During the test, a list of 15 monosyllabic words is read aloud by the examiner for 5 times. After each trial, the subject is asked to repeat the words he or she remembers. After fifteen minutes with other questions, delayed recall is assessed by asking the participant which words he or she still remembers. At baseline and after 12 months the same version of the test is administered and after six months a parallel version with 15 different words is administered.

- Verbal Fluency Test (VFT) [59]**:** this is a measure of expressive language. If language is intact, the VFT is also a measure of executive functioning. The subject is given a letter and is asked to name words beginning with the particular letter in one minute. In one administration of the test three letters are given. At the six and 12 months follow up measurements parallel versions with different letters are administered.

- Digit Symbol Substitution Test (DSST) [60]***:*** this is a measure of attention, perceptual speed, motor speed, visual scanning and memory. The subject is given a piece of paper with nine symbols corresponding with nine digits. Next on this piece of paper are three rows of digits with empty spaces below them. The subject is asked to fill in as many corresponding symbols as possible in 90 seconds.

- Abridged Stroop Colour Word Test (SCWT-A) [61]**:** this is a measure of complex processing. The SCWT-A consist of three tasks; 1) word reading, 8 rows of 5 written colours; 2) colour naming, naming the colours of 8 rows of 5 red, green, blue or yellow coloured rectangles; 3) combination task, the words *red*, *green*, *blue* and *yellow* have been printed in a different colour of ink, the subject is asked to name the colour of the ink.

- Informant questionnaire on cognitive decline (IQ-code) [62,63]**:** a significant other of the participant is asked to answer 16 questions about changes in the participant's cognitive function during the last ten years.

Secondary outcome measures

Three interviewer administered questionnaires are used to complete the picture of quality of life. Only the geriatric depression scale is self administered.

Quality of life

- ***Short Form 12 (SF-12)***[64]: the SF-12 is a measure of health status consisting of twelve items measuring eight concepts of both physical and mental health. The physical and mental component summary scales are scored using norm-based methods.
- ***Dementia Quality of Life (D-QoL)***[65]: the D-QoL is a 29 item measure especially developed for elderly people with cognitive decline and dementia. Five domains are measured: self esteem, positive affect/humour, negative affect, feelings of belonging and sense of aesthetics. The response scale is a five point scale with higher score indicating better quality of life.
- ***Euro Quality of Life (Euro-QoL)***[66]**:** the Euro-QoL questionnaire is a standardised measure for general health status measuring five dimensions: mobility, self care, usual activities, pain/discomfort and anxiety/depression. The participant is asked to choose from three response categories for each dimension. By composing a five digit number consisting of the three response categories on the five dimensions, participants can be classified into one of 243 defined health states.
- ***Geriatric Depression Scale (GDS)***[67]**:** the GDS is a self administered depression scale for older adults. The short version is used in which participants are asked to report how they felt the last week by answering 15 yes/no questions. The maximum score is 15, and a score over five points is suggestive of depression.

Physical activity and aerobic fitness

- ***Physical activity level:*** the LASA physical activity questionnaire[55] is administered during the face-to-face interview to determine the physical activity level of the participants. Participants are interviewed about their physical activities during the last two weeks by asking questions about the frequency and duration of different activities (e.g. housekeeping, sports activities, cycling, gardening). Their answers are converted to an overall physical activity score expressed in minutes of physical activity per day.
- ***Accelerometer***: a random sample of participants of each of the four intervention groups is asked to wear an accelerometer (ActiGraph, activity monitor) for three days. Data will be used to compare the level of activity in participants in the walking program and in the placebo activity group.
- ***Aerobic fitness:*** aerobic fitness is assessed in a sports hall, using the walking test of the Groningen Fitness test for the elderly.[68] This is a sub-maximal test for aerobic endurance in

which participants walk distances of 16.6 metres between pylons in a large rectangle of 16.6 by 8.3 metres. For every walked distance, a score of one point is given. To increase their score, adults have to be within a three metre distance of the next pylon before a signal sounds. A double signal sounds when walking speed is increased. Walking speed is increased every three minutes with one kilometre, starting with a walking speed of four kilometres per hour to a maximum walking speed of seven kilometres per hour. If a participant fails twice to reach the next pylon in time, the test is finished for that particular participant. The maximum score of 66 points corresponds to a total walking distance of 1.1 kilometres.

Physical measures

- ***Anthropometric measurements:*** in order to calculate *body mass index* (kg/m^2), body height and body weight are measured during the break in the face-to-face interview. *Blood pressure* is measured electronically (Omron M5-1) after five minutes of rest during the face-to-face interview. Participants with a diastolic blood pressure exceeding 95 and a systolic blood pressure exceeding 160 are offered to have their blood pressure measured again by a geriatrician. If hypertension is diagnosed, the participant will be treated.
- ***Homocysteine and vitamin B concentrations***: non-fasting blood samples are taken at the laboratory of the Medical Center Alkmaar. Homocysteine concentrations in plasma and folate and vitamin B12 concentrations in serum are determined by a competitive immunoassay using direct chemiluminescent technology (ADVIA CENTAUR, Bayer Corporation, Tarrytown, USA). For determination of red blood cell folate, hemolysates are prepared out of EDTA plasma and ascorbic acid. Folate concentrations in erythrocytes is determined in the hemolysate by a competitive immunoassay using direct chemiluminescent technology (ADVIA CENTAUR, Bayer Corporation, Tarrytown, USA). According to the manufactures instructions, folate in erythrocytes is calculated using the following algorithm: folate in hemolysate X 21 minus folate in serum X ((100 – hematocrit) / (hematocrit * 100)). Vitamin B6 in plasma is determined by high performance liquid chromatography with fluorescence detection using Chrompack Lichrosorb RP-18 columns (Varian Inc., Palo Alto, USA) and the Jasco HPLC system (Jasco Benelux, Maarssen, The Netherlands).

Statistical analysis

Analysis will focus upon estimating the effect of both interventions on four domains: 1) cognition; 2) quality of life; 3) aerobic fitness and habitual physical activity levels; and 4) homocysteine and vitamin B concentrations. The effect of physical activity and FA/B12/B6 supplementation will be examined independently from each other as we do not expect an

interaction between these interventions. Before analysis are performed, comparability at baseline of the intervention groups will be examined. If necessary, analysis will be adjusted for baseline differences. Subsequently, the data set will be analysed according to the 'intention-to-treat' and according to the 'per protocol' principle. The difference between the walking program and the placebo activity program, and between the verum and placebo supplements will be assessed using linear regression. The dependent variables will be values after six and 12 months in the four before mentioned domains. Both interventions will be independent variables. Moreover, regression analysis will be adjusted for baseline values and possibly confounding covariates, such as gender and age. Also, interaction between gender and the interventions will be investigated using interaction terms.

DISCUSSION

The literature provides promising results on the beneficial effect of physical exercise and supplementation with folic acid, vitamins B12 and B6 on cognitive function and quality of life both in cognitive healthy as well as in the demented elderly people. However, to our knowledge, no large intervention study has been conducted yet on the effect of these interventions on cognition decline in subjects with MCI. In the RCT described in this paper, the effects on cognition and quality of life will be examined in a sample of community-dwelling elderly people aged 70 to 80 years. A factorial design is used and it is assumed that the interventions have an independent effect. We hypothesise that both exercise and FA/B12/B6 supplementation beneficially influence cognitive function and quality of life in this particular group of subjects. The results of this trial will provide clinicians in the field of ageing with more knowledge about treatment of older persons with cognitive decline. If proven effective, exercise and vitamin supplementation are an additional intervention method for this target group. Implementation of the walking program in The Netherlands is relatively easy, since infrastructure for group based exercise programs for older adults already exists. Vitamin supplementation is easy to implement as well. The most difficult aspect might be long term compliance in case of severe cognitive decline. However, compliance can be sustained by providing methods to remember taking the vitamin supplements. An additional important advantage of both interventions is that involvement of the clinician is limited to prescribing exercise and vitamin supplementation, and possibly to evaluate compliance at future medical check-ups.

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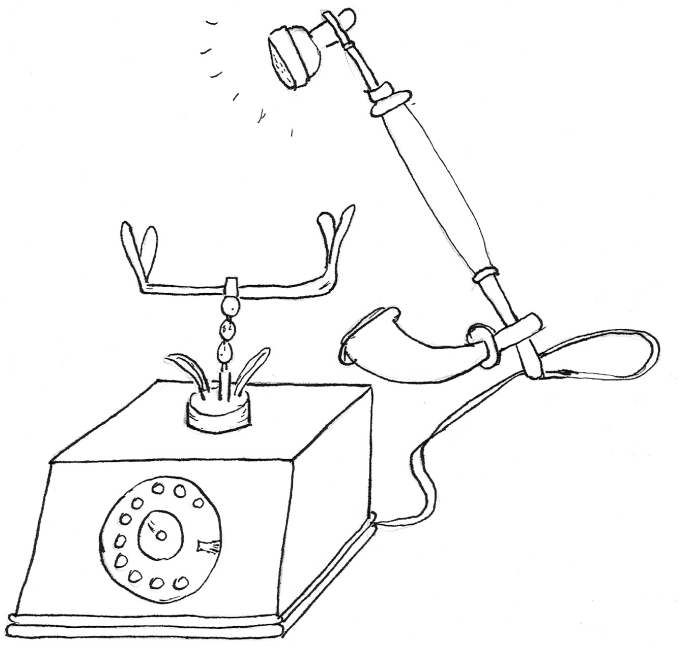
4

Detection of memory impairment in the general population: screening by questionnaire and telephone compared with subsequent face-to-face assessment



JGZ van Uffelen, MJM Chin A Paw, M Klein, W van Mechelen, M Hopman-Rock. Int J Geriatr Psychiatry 2007;22:203-210

ABSTRACT

Background

Development of efficient methods for identifying subjects with Mild Cognitive Impairment (MCI) from the general population is warranted, because these subjects represent an important group for (epidemiological) research purposes. Objectives: 1) To describe a two-step population screening for identifying adults with MCI from the general population for research purposes, by questionnaire and telephone; 2) To compare screening by telephone (method one) to a subsequent face-to-face assessment (method two).

Methods

In method one, subjects with memory complaints were identified from the general population (n= 5491) by a postal questionnaire. Subsequently, cognitive status and memory were assessed in a telephone interview using the Telephone Interview for Cognitive Status and the 10 Word Learning Test. Next, subjects with MCI according to method one were subjected to a face-to-face assessment for method two, in which cognitive status and memory were assessed using the Mini Mental State Examination (MMSE) and the Auditory Verbal Learning Test (AVLT).

Results

Two hundred and twenty-seven subjects completed both the telephone interview and the face-to-face assessment. Ninety-three subjects (41%) had MCI according to both methods. Seven subjects (3%) failed to meet MCI criteria according to method two because of an MMSE score < 24; 127 subjects (56%) failed because of normal AVLT scores.

Conclusion

1) The two-step population screening was able to detect a considerable number of MCI-subjects in the general population; 2) agreement between both methods was moderate. Therefore, the method of recruiting subjects for (epidemiological) studies has to be taken into consideration when interpreting results of these studies.

INTRODUCTION

Society of the future will be a doubly ageing one, because of increasing numbers of elderly people, who will also grow older than before. This phenomenon will be associated with all concomitant burdens of degenerative chronic diseases[1,2], such as dementia. According to the WHO, by the year 2020 there will be almost 29 million demented adults worldwide.[3] These adults will put both a substantial financial burden on healthcare systems, as well as a personal burden on their significant others. Therefore, selecting possible target groups for the prevention of cognitive decline has consequently become an important issue in the field of cognitive ageing research.[4]

In this respect, increasing attention has been paid in particular to the concept of amnestic Mild Cognitive Impairment (MCI). MCI refers to a potential transitional stage in which persons experience memory loss to a greater extent than is expected for age, but do not meet clinical criteria for Alzheimer's disease (AD).[5] Although several MCI criteria have been suggested[2,6], the Petersen criteria[7] are the most widely used: 1) memory complaints; 2) impaired memory; 3) normal mental status; 4) normal daily function; and 5) not demented. Since MCI criteria have been operationalised using different neuropsychological outcome measures and/or cut-off points, prevalence reports of MCI in the general population differ and range from three to 19 percent.[8-10] Although it is possible for individuals with MCI to remain stable or recover, it is generally agreed upon that compared with cognitively healthy adults they have an increased risk to convert to AD. Reported conversion rates to AD vary from approximately eight to 41 percent per year.[7,9,11-14]

As the stage of MCI is the optimum stage to intervene with potentially preventive therapies to prevent conversion to dementia[15], for research purposes, the development of efficient methods suitable for identifying subjects with MCI from the general population is warranted. While face-to-face neuropsychological assessment is commonly used, its main limitation is that it is time consuming. In this respect, telephonic cognitive screening instruments that are able to discriminate between normal and dementing elderly people are readily available.[16,17] Because screening over the telephone enables researchers to reach large groups of elderly people in a relatively short time period, this seems an attractive alternative.

The aim of this study is twofold: 1) To describe a two-step population screening for identifying MCI-subjects by questionnaire and telephone from the general population for participation in a randomised controlled trial; 2) To compare screening by telephone to a subsequent face-to-face assessment with respect to the number of identified MCI-subjects.

METHODS

Study design

The two-step population screening was developed to identify MCI-subjects from the general population for participation in a Randomised Controlled Trial (RCT).[18] In the present study, the two-step population screening (method one) is described and compared with a subsequent face-to-face assessment (method two). Operational criteria for MCI according to both methods are described in Table 1. First, subjects with memory complaints were identified by a postal questionnaire. Subsequently, cognitive status and memory were assessed in a telephone interview. Next, only MCI-subjects according to method one, were subjected to the subsequent face-to-face assessment.

TABLE 1: Petersen criteria for MCI and operationalisation in both methods

Petersen MCI criteria	Method one	Method two
1. Memory complaints	yes to question 'do you have memory complaints', or at least twice 'sometimes' at cognition scale of Strawbridge	-
2. Objective memory impairment	10 WLT delayed recall ≤ 5 + percentage savings ≤ 100	AVLT delayed recall ≤ 1SD
3. Normal mental status	TICS ≥ 19	MMSE ≥ 24
4. Intact daily function	no report of disability in activities of daily living on GARS-scale, except on the item 'taking care of feet and toe nails'	-
5. Absence of dementia	TICS ≥ 19	MMSE ≥ 24

MCI= Mild Cognitive Impairment; Method one= Two-step population screening; Method two= Face-to-face assessment; 10 WLT= 10 Word Learning Test; AVLT= Auditory Verbal learning Test; TICS= Telephone Interview for Cognitive Status; MMSE= Mini Mental State Examination; GARS= Groningen Activity Restriction Scale

Subjects

All community-dwelling adults in a medium-sized Dutch town aged 70 to 80 years (n= 5491) received study information and a postal questionnaire by mail. Their addresses were obtained from the register of the municipality. The study protocol, including the recruitment of participants, was approved by the VU University Medical Center ethics committee. Informed consent was obtained prior to the start of the study.

Method one: two-step population screening

1. Postal questionnaire

The aim of the questionnaire was to select subjects with memory complaints and unaffected Activities of Daily Living (ADL) for the subsequent telephone interview and to check eligibility for an RCT[18] by addressing other inclusion criteria (Table 2). Memory complaints were assessed in two ways. First, subjects were asked if they had memory problems (yes/no). Additionally, the cognitive domain of the Strawbridge scale was administered.[19] This scale consists of four questions concerning self-perceived cognitive function (difficulty paying attention, trouble finding the right word, difficulty remembering things, forgetting where something was put). Response categories were: never, sometimes, often, and very often. ADL function was assessed using the Groningen Activity Restriction Scale (GARS).[20] This scale consists of eleven questions concerning ADL and seven questions concerning instrumental ADL. Subjects were asked if they were able to perform these activities easily, with difficulty or not at all. They were considered as having intact ADL functioning if they reported no disabilities on the ADL items.

2. Telephone interview

The aim of the telephone interview was to assess mental status and memory performance. Mental status was assessed using the Telephone Interview for Cognitive Status (TICS)[21], which examines the most important aspects of cognitive function (orientation, concentration, memory, naming, comprehension, calculation, reasoning, judgment and praxis). The score ranges from 0 to 41, with a higher score indicating better cognitive function. Memory performance was assessed using a Dutch version of the 10 Word Learning Test (10 WLT).[22] The 10 WLT measures immediate and delayed memory. The examiner reads aloud a list of ten words (trial 1) and after hearing the list, the participant is asked to repeat the words he or she remembers. This procedure is repeated two more times (trial 2 and 3). Five minutes later, delayed recall is assessed by asking the participant to recall the words, leading to a maximum recall score of ten words. Percentage savings is defined as the number of recalled words as a percentage of the score in the third trial. The telephone interview was performed by trained interviewers and took at most 15 minutes.

Those with MCI as determined by method one:

- Answered 'yes' to the broad memory complaint question, OR
- Answered at least 'sometimes' on two or more of the four Strawbridge questions, AND
- Reported no disabilities in activities of daily living on the GARS-scale, AND
- Met eligibility criteria for the RCT as mentioned in Table two, AND
- Scored ≥ 19 on the TICS, AND
- Had a delayed recall score ≤ 5/10 on the third trial of the 10 WLT (this applied cut-off point for memory impairment corresponds with one standard deviation below normal performance[23] and is in accordance with other population studies[9,24] AND
- Had an absolute percentage savings ≤ 100 percent.

TABLE 2: Selection criteria for telephone screening

Criteria for MCI (1-2) and other inclusion criteria for the RCT (3-9)
1. Self reported memory complaints (answer 'yes' to question 'do you have memory complaints', or at least twice 'sometimes' on the cognition scale of Strawbridge)
2. No report of disability in activities of daily living on GARS-scale, except on the item 'taking care of feet and toe nails'
3. Being able to perform physical activities of moderate intensity, without making use of walking devices, e.g. a rollator or a walking frame
4. Not using vitamin supplements/vitamin injections/drinks with dose of folic acid, vitamins B12 or B6 comparable to the vitamin supplement given in intervention
5. Not suffering from epilepsy, multiple sclerosis, Parkinson's disease, kidney disorder requiring haemodialysis, psychiatric impairment
6. Not suffering from depression as measured by the GDS (cut off ≤ 5)
7. Not using medication for rheumatoid arthritis or psoriasis interfering with vitamin supplement
8. No alcohol abuse (men < 21 consumptions a week, women < 15 consumptions a week)
9. Not currently living in a nursing home or on a waiting list for a nursing home

MCI= Mild Cognitive Impairment; RCT= Randomised Controlled Trial; GARS= Groningen Activity Restriction Scale; GDS= Geriatric Depression Scale

Method two:

face-to-face assessment for those meeting MCI criteria according to method one

During this face-to-face assessment, mental status and memory were assessed using respectively the Mini Mental State Examination (MMSE)[25] and the Auditory Verbal Learning Test (AVLT).[26] The Dutch modification of the AVLT was used to assess memory. The principle of the AVLT is similar to the 10 WLT administered during the telephone interview, but the AVLT consists of 15 words and 5 trials for immediate recall. Delayed recall is measured after 20 minutes of non-memory related questions. The face-to-face assessments were administered by trained interviewers who were blind to the participant's performance during the telephone screening. During the face-to-face assessment, performance on other

neuropsychological measures was assessed to provide a further description of the population. The Digit Symbol Substitution Test measures attention, perceptual speed, motor speed, visual scanning and memory.[27] The Verbal Fluency Test measures expressive language.[28] The Abridged Stroop Colour Word Test is a measure of complex processing.[29] These measures have been described in detail elsewhere.[18]

Those with MCI as determined by method two:

- Had an MMSE score ≥ 24, AND
- Had an AVLT delayed recall score of 1 SD or more below the mean of healthy controls.

Agreement between both methods

Finally, the percentage of agreement between both methods was examined. The subjects therefore fell into three groups:

- Those meeting MCI criteria according to both methods,
- Those who failed to meet MCI criteria of method two because of an MMSE score < 24,
- Those who failed to meet MCI criteria of method two because of an AVLT performance better than 1 SD below the mean of healthy controls.

Data analysis

SPSS, version 12.0.1, was use for data analysis. P-values < 0.05 were considered statistically significant. First, subjects fulfilling MCI criteria according to method one and subjects not fulfilling these criteria were compared regarding sociodemographic characteristics and TICS and 10 WLT performance. Differences were tested using independent student's T-tests, Mann Whitney U tests and Chi-square tests. To detect the number of MCI-subjects according to method two, the number of subjects performing worse than 1 SD below the mean of the AVLT was determined. This was done by translating AVLT recall scores into Z-values adjusted for age, gender and education using regression analysis as derived from the normative sample.[30] Subsequently, the percentage of agreement between both methods was examined.

RESULTS

In September 2003, questionnaires were sent to 5491 community-dwelling adults aged 70 to 80 years. The response rate was 36 percent (n= 1953), of which 1487 subjects wanted to participate. After applying inclusion criteria for the RCT (Table 2), 569 adults were eligible for the telephone interview. The telephone interview was administered to 495 subjects. Due to various reasons no telephone interview was available from 74 subjects. Of the 495 subjects who completed the telephone interview, 249 had MCI according to method one (Figure 1) and 246 had not. In addition to the expected significant differences between subjects with and without MCI according to method one in TICS and WLT 10 performance, MCI-subjects were significantly more often men, had a lower educational level and were more often living with a partner (Table 3).

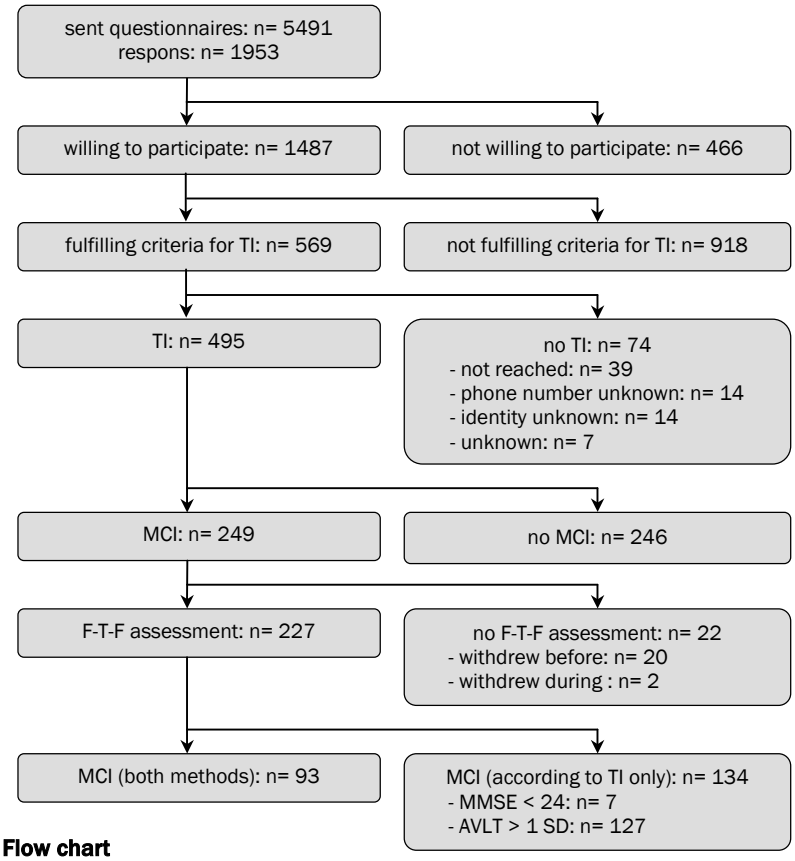


FIGURE 1: Flow chart

TI= Telephone Interview; MCI= Mild Cognitive Impairment; F-T-F assessment= Face-To-Face assessment; MMSE= Mini Mental State Examination; AVLT= Auditory Verbal Learning Test

TABLE 3: Characteristics of subjects with and without MCI according to method one

Mean values (SD), unless indicated otherwise	MCI N= 249	No MCI N= 246	Total group N= 495
Age (years)	75.0 (3.0)	74.6 (2.8)	74.8 (2.9)
Gender (% male)*	56.6	38.8	47.8
Education (% low/intermediate/high)[a]*	57/ 27/ 17	42/ 36/ 22	49/ 31/ 19
Marital status (% living with a partner)*	69.1	54.7	61.9
TICS†	31.8 (3.4)	34.2 (2.9)	33.0 (3.3)
Immediate recall 10 WLT†	15.3 (3.3)	20.7 (3.9)	18.0 (4.5)
Delayed recall 10 WLT†	3.7 (1.3)	7.1 (1.3)	5.4 (2.2)
Percentage savings†	60.1 (22.1)	89.3 (22.0)	74.6 (26.4)

MCI= Mild Cognitive Impairment; Method one= Two-step population screening; SD= Standard Deviation; TICS= Telephone Interview for Cognitive Status; 10 WLT= 10 Word Learning Test; [a] *low*= No education, primary education, lower vocational training, *intermediate*= intermediate level secondary education, intermediate vocational training, *high*= higher level secondary education, higher vocational training, university training; * $p < 0.01$, X^2 test; † $p= 0.00$, T-test (difference between MCI and no MCI)

The face-to-face assessment was completed by 227 of the 249 MCI-subjects according to method one. Twenty subjects withdrew after receiving the invitation for the face-to-face assessment due to various reasons, e.g.: too busy, only wanted to participate with a not for the study selected partner. Two subjects withdrew during the face-to-face assessment. Of these 227 subjects, 93 (41%) met the criteria for MCI according to both methods. Consequently, the other 134 subjects only met MCI criteria according to method one; seven of them (5%) did not meet MCI criteria according to method two because of an MMSE score < 24. One of these subjects had a normal AVLT score and was counted in the MMSE < 24-group only. Of the remaining 127 subjects (95%), the AVLT performance was too good to be classified as having MCI according to method two. These 127 subjects performed significantly better on the AVLT delayed recall than subjects in the other two groups (Table 4).

TABLE 4: Characteristics and cognitive test performance of subjects classified with MCI according to both methods and of subjects classified with MCI according to method one only

Mean values (SD), unless indicated otherwise	MCI (both methods) N= 93	MCI (method one only, MMSE < 24) N= 7	MCI (method one only, AVLT > 1 SD) N= 127
Age	75.3 (3.0)	76.3 (3.0)	75.2 (2.8)
Gender (% male)	61	100	56
Education (% low/intermediate/high)[a]	57/28/15	86/0/14	53/26/21
Marital status (% living with a partner)	72	100	68
MMSE (Median (10^{th}; 90^{th} ‰))*	28 (24; 30)	21 (17; 23)	29 (27; 30)
AVLT immediate recall†	26.0 (6.6)	18.9 (5.0)	36.3 (6.3)
AVLT delayed recall†	3.3 (1.6)	2.0 (1.6)	7.3 (1.8)
Other neuropsychological measures			
Stroop Word [b]†	21.2 (6.0)	28.0 (9.4)	19.7 (4.3)
Stroop Colour [b]†	28.4 (8.6)	41.3 (20.9)	25.9 (4.9)
Stroop Colour/Word[b]†	69.3 (23.4)	97.9 (30.4)	60.0 (19.9)
DSST†	35.1 (11.2)	22.9 (8.6)	36.2 (9.7)
VFT‡	28.0 (10.2)	20.3 (14.5)	30.8 (10.0)

MCI= Mild Cognitive Impairment; Method one= Two-step population screening; Method two= Face-to-face assessment; MMSE= Mini Mental State Examination; AVLT= Auditory Verbal Learning Test; DSST= Digit Symbol Substitution Test; VFT= Verbal Fluency Test; [a] *low*= No education, primary education, lower vocational training, *intermediate*= intermediate level secondary education, intermediate vocational training, *high*= higher level secondary education, higher vocational training, university training; [b] Lower score indicates better performance; * p= 0.00, Kruskal Wallis Test; † p= 0.00, one-way ANOVA; ‡ p < 0.05, one-way ANOVA

DISCUSSION

In order to identify large numbers of subjects with MCI for research purposes, efficient and inexpensive methods for population screening need to be developed. In the present study, a two-step population screening for identifying older adults with MCI from the general population by postal questionnaire and a telephone interview is described. Moreover, screening by telephone (method one), was compared with a subsequent face-to-face assessment (method two).

The percentage of agreement between both methods was 41 percent. This is in concordance with the study of Lines et al.[31], in which an agreement of 43 percent was found. In that study, also more men than women met MCI criteria. In contrast to their findings, in our study, subjects with MCI were lower educated than subjects without MCI. However, in general, higher educated individuals perform better on cognitive tests.[28]

The observed moderate agreement may have been caused by various reasons. Even though our cut-off point for the TICS was lower than advised[21], only seven subjects out of 227 had an abnormal MMSE score in combination with a normal TICS score. Thus, the moderate agreement between the methods can be attributed mainly to differences in performance on the 10 WLT and the AVLT. All selected subjects had a 10 WLT delayed recall score of one standard deviation below the mean in the telephone interview, but 56 percent of them had a normal performance on the AVLT during the face-to-face assessment. First, this may have been caused by the experience of the subjects with the conceptual basis of the test. Due to their experience with the 10 WLT during the telephone interview, subjects may have expected to recall the AVLT word list during the face-to-face assessment. Secondly, differences between the telephone and the face-to-face assessment may have existed regarding feelings of being at ease and audibility. However, in another study comparing telephone and in person assessment of verbal memory, no difference in performance was found.[32] Finally it can be questioned whether the 10 WLT and the AVLT measure aspects of memory to the same extent, because both word learning tasks differ with respect to the number of words, the number of trials for immediate recall and the retention time.

Limitations of the study

In the present study, only MCI-subjects according to method one were subjected to the subsequent face-to-face assessment. As a consequence, no data are available on sensitivity and specificity of the telephone screening compared with the face-to-face assessment. Since there is no gold standard for diagnosing MCI, the estimation of sensitivity and specificity would have been difficult in any case. Moreover, methods for population screening for identifying subjects for trials do not need to be highly sensitive by clinical standards as their purpose is to provide a group of individuals with an increased risk for cognitive decline.

Also, no comprehensive clinical examinations of subjects identified as having MCI according to both methods are available, because this could not be realised for financial and time reasons. Certainly, the two-step population screening alone will not suffice to provide clinical individual diagnoses. Clinical screening includes elaborate measures such as neuro-imaging, and judgment of a clinician, while for epidemiological research often solely neuropsychological examination is feasible. However, even though we did not primarily intend to develop a diagnostic tool applicable in clinical practice, one could use the described screening to select a population with a preponderance of individuals with MCI for further detailed screening. Our two-step population screening was successful in doing so, because by applying it, the percentage of subjects with MCI increased from three to four

percent in the general population[9] to 41 percent in subjects selected by the two-step population screening. Therefore, the results of the present study may also be of interest with regard to the development of urgently needed cost-effective instruments for clinical purposes. Obviously, for clinical purposes, sensitivity and specificity are very important issues, which have to be further addressed in future research. Meanwhile, the identification of older adults with MCI from the general population for clinical (research) purposes can be done e.g. by general practitioners using observation instruments, such as the Observation List for Early signs of Dementia.[33]

In sum, the described two-step-population screening can be used for identifying a population with a large preponderance of individuals with MCI. For research purposes, such a population could be useful e.g. for randomised controlled trials where the diagnostic error of the tests would presumably be balanced across various groups assigned to different kinds of interventions, or where a lower 'yield' of true prodromal Alzheimer's disease would simply mean that larger numbers must be enrolled. For clinical purposes, one could use the method described here to provide a population for further detailed screening for a 'purer' group of individuals with MCI according to clinical criteria.

CONCLUSION

Since the concept of MCI is operationalised in many different ways, the cognitive qualities of subjects defined as MCI-patients can differ considerably between studies. For this reason, the method of identification of MCI has to be taken into consideration when interpreting results of studies targeting subjects with MCI. Our two-step population screening was able to detect a considerable number of MCI-subjects in the general population. Moreover, because telephone screening is fast, easy to apply and inexpensive, it should be considered as a valuable tool to be used in future cognitive ageing studies in which large groups of subjects at risk for cognitive decline have to be detected at an early stage.

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5

Effectiveness of physical exercise and vitamin B supplementation: a randomised controlled trial in community-dwelling older adults with mild cognitive impairment

5.1

The effect of walking and vitamin B supplementation on cognition in community-dwelling older adults with mild cognitive impairment

JGZ van Uffelen, MJM Chin A Paw, W van Mechelen, M Hopman-Rock
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ABSTRACT

Objectives

To examine the effects of a walking program and vitamin B supplementation on cognitive function.

Design, participants and setting

Randomised, double-blind, placebo-controlled trial with a factorial design. Participants were 152 community-dwelling subjects with Mild Cognitive Impairment (MCI). The setting was the general population

Interventions and measurements

Participants were randomly assigned to one year of: 1) a twice-weekly, group-based, moderate-intensity walking program (WP, n= 77) or a low-intensity placebo activity program (n= 75); and 2) daily vitamin pills containing 5 mg folic acid, 0.4 mg B12, 50 mg B6 (FA/B12/B6, n= 78) or placebo pills (n= 74). Outcome measure was cognitive function, measured with neuropsychological tests at baseline and after six and 12 months.

Results

Mean age (SD) of the participants was 75 (2.9) years and 56 percent (n= 85) were male. Median adherence to the exercise programs (25^{th}; 75^{th} percentile) was 63 (2; 81) percent and median compliance with taking pills (25^{th}; 75^{th} percentile) was 100 (99; 100) percent. Intention-to-treat analysis revealed no main intervention effect of both interventions. In women in the WP, complex processing (stroop combination task) improved by 0.3 seconds (p= 0.04) and delayed recall (auditory verbal learning test) by 0.04 words (p= 0.06) with each percent increase in adherence. Analysis in men attending at least 75 percent of the sessions showed improvement of delayed recall in men in the WP (beta [95%CI]= 1.5 [0.1; 3.0] words).

Conclusion

Vitamin B supplementation and walking were not effective in improving cognition within one year. Increased adherence to the walking program, however, appeared to have a beneficial effect on memory in men and on memory and complex processing in women.

INTRODUCTION

Cognitive impairment is a very important public health concern, since the number of elderly people with age-related health problems such as cognitive decline and dementia is growing considerably. For this reason, research on potentially effective interventions for preventing the progression of cognitive impairment is warranted. Effective interventions would greatly benefit both individuals and society in general. In this respect, physical exercise and vitamin B supplementation seem promising and relatively inexpensive interventions.

The stage of Mild Cognitive Impairment (MCI) seems the most appropriate stage at which to intervene.[1] MCI represents a potential transitional stage in which persons experience memory loss to a greater extent than is expected for age and education, but do not meet criteria for Alzheimer's disease. Most widely used criteria for MCI are those of Petersen[2]: 1) subjective memory complaint; 2) objective memory impairment; 3) normal mental status; 4) intact activities of daily living; and 5) no dementia.

Regular exercise is associated with better cognitive function and delayed onset of Alzheimer's disease.[3-6] Moreover, physical activity and exercise were found to improve cognitive function in cognitively healthy and demented older adults.[7,8] The specific mechanisms of exercise beneficially affecting cognitive performance in subjects in different stages of cognitive decline are not yet known, but improvement of vascularisation and increased blood flow to the brain are possible pathways, which may be promoted by improving aerobic fitness.[9,10]

Low concentrations of folic acid, vitamins B12 and B6 result in increased concentrations of the amino acid homocysteine[11], which is negatively associated with various domains of cognition.[12-16] Negative associations have also been observed in the presence of normal homocysteine concentrations.[17] However, few long-term methodologically strong trials have examined the effect of vitamin B supplementation on cognition.[18-20] It was hypothesised that vitamin B supplementation affects cognitive performance via two mechanisms.[21] First, vitamin B is needed to transform homocysteine into methionine, which is an essential amino acid for the central nervous system. A lack of methionine will finally result in disorders in neurological and psychological status. The second mechanism assumes a beneficial influence on homocysteine concentrations, resulting in structural vascular changes in the brain.

In the present study, the effects of one year of a moderate intensity walking program designed to improve aerobic fitness, and one year of daily supplementation with folic acid, vitamins B12 and B6 on cognitive performance of community-dwelling older adults with mild cognitive impairment were examined. It was hypothesised that both interventions would beneficially influence cognitive performance.

METHODS

Study design

Double-blind randomised controlled trial (RCT) with a two-by-two factorial design. The study-protocol has been described elsewhere[22] and was approved by the medical ethics committee. Written informed consent was obtained from all participants.

Participants

All community-dwelling inhabitants 70 to 80 years of age in a Dutch town (n= 5491) were sent an invitation letter in September 2003. Of those willing to participate in the RCT, subjects with MCI were identified using a two-step screening consisting of a postal questionnaire and a telephone interview in which inclusion criteria were checked.[23] Operational criteria for MCI and additional inclusion criteria for the trial are described in Table 1.

Randomisation and blinding

After the baseline interview, participants were randomised using the option 'random sample of cases' in SPSS. Randomisation was stratified for physical activity level as measured by the LASA physical activity questionnaire.[24] Intervention groups were: 1) walking program or placebo activity program; and 2) vitamin B supplementation or placebo supplementation. Participants and exercise instructors were blinded to group allocation by being left unaware of which exercise program was supposed to be effective. The pills were coded as A or B by the manufacturer. The key was decoded after data-analysis. All cognitive outcome measures were assessed by trained examiners, who were also blinded to group allocation.

Interventions

Walking program (WP) and Placebo activity program (PAP)

Both the WP and the PAP were group-based and lasted one year (June 2004 – June 2005). Frequency was twice a week and session duration was 60 minutes. Sessions were supervised by trained instructors.

TABLE 1: Inclusion and exclusion criteria for participation in the trial

Operationalisation of Petersen criteria for MCI (1-5) and additional inclusion criteria for the RCT (6-12)
1. Memory complaints (answer yes to question 'do you have memory complaints', or at least twice sometimes at cognition scale of Strawbridge[25])
2. Objective memory impairment; 10 WLT[26] delayed recall ≤ 5 + percentage savings ≤ 100
3. Normal general cognitive functioning; TICS[27] ≥ 19 + MMSE[28] ≥ 24
4. Intact daily functioning: no report of disability in activities of daily living on GARS-scale[29], except on the item 'taking care of feet and toe nails'
5. Absence of dementia; TICS ≥ 19 + MMSE ≥ 24
6. Being able to perform moderate intensity physical activity, without making use of walking devices, e.g. a rollator or a walking frame
7. Not using vitamin supplements/ vitamin injections/ drinks with dose of folic acid, vitamins B12 or B6 comparable to vitamin supplement given in intervention
8. Not suffering from epilepsy, multiple sclerosis, Parkinson's disease, kidney disorder requiring haemodialysis, psychiatric impairment
9. Not suffering from depression as measured by the GDS[30] (cut-off ≤ 5)
10. Not using medication for rheumatoid arthritis or psoriasis interfering with vitamin supplement
11. No alcohol abuse (men < 21 consumptions a week, women < 15 consumptions a week)
12. Not currently living in a nursing home or on a waiting list for a nursing home

MCI= Mild Cognitive Impairment; RCT= Randomised Controlled Trial; 10 WLT= 10 Word Learning Test; TICS= Telephone Interview for Cognitive Status; MMSE= Mini Mental State Examination; GARS= Groningen Activity Restriction Scale; GDS= Geriatric Depression Scale

Adherence was defined as the percentage of attended sessions. Based on an existing aerobic walking program designed to improve aerobic fitness[31], intensity of the WP was moderate (> 3 metabolic equivalents). Each session consisted of a warm-up, moderate-intensity walking exercises and cool-down. The intensity was increased gradually during the program by increasing the walking-pace and distance. Sessions took place outdoors in municipal parks. The PAP, developed by four exercise instructors experienced with older adults, consisted of an introduction, low-intensity (< 3 metabolic equivalents) non-aerobic group exercises and a closing. Sessions were divided into five themes: relaxation, activities of daily living, balance, flexibility, posture and a combination. For each theme, three sessions were developed and the series of 18 sessions was repeated during the intervention. The PAP was carried out in community centres.

Vitamin B supplementation (FA/B12/B6) and placebo supplementation

Participants randomised to FA/B12/B6 received one pill daily, containing 5 mg vitamin B11 (Folic Acid), 0.4 mg vitamin B12 (Cyanocobalamin) and 50 mg vitamin B6 (Pyridoxine-hydrochloride) for a year. These vitamin supplements are available on prescription in The Netherlands. For the purpose of this study, the package and vitamin pills could not be identified as an existing supplement. Participants in the control group received an identical-

looking placebo pill. Pills were packed in one-week blister packs that were labelled for each day of the week. Compliance was verified by counting pills in returned blister packs.

Outcome measures

Measurement of baseline variables has been described elsewhere.[22] Cognitive outcome measures were collected at baseline and after six and 12 months during a standardised interview. The Mini Mental State Examination (MMSE) was used to measure mental status. The maximum score is 30, and a score below 24 was considered abnormal.[32] The Auditory Verbal Learning Test (AVLT) was used to assess immediate and delayed recall (maximum scores 75 and 15 words, respectively).[33] To assess expressive language, the verbal fluency test (VFT) was administered, in which participants were asked to name words starting with a particular letter during a one-minute period. In each administration of the test, three letters were given. The score was the total number of named words.[34] The Digit Symbol Substitution Test (DSST) was used to measure perceptual speed and motor speed. The participant was asked to draw symbols corresponding to nine digits below numbered boxes during a 90-second period. The score was the number of correctly drawn symbols.[35] The Abridged Stroop Colour Word Test (SCWT-A) was administered to assess complex processing. The SCWT-A consists of three tasks; 1) reading eight rows of five written colours; 2) naming the colours of eight rows of five red, green, blue or yellow coloured rectangles; 3) naming the colour of ink for the words *red*, *green*, *blue* and *yellow*. The score was the time needed to complete each task.[36]

Statistical analysis

Sample size

The sample size calculation was based on data from Petersen et al.[2], who compared performance on cognitive tests of four groups, i.e. subjects without cognitive decline, subjects with MCI, subjects with mild Alzheimer's disease (AD) and subjects with AD. Because memory was the most important cognitive outcome in our study, AVLT data were used. The average difference in AVLT performance between subjects with MCI and mild AD and subjects with MCI and AD was considered to be significant. Since Petersen et al. did not report the absolute number of words as a measure of delayed recall, our sample size calculation was based on the absolute number of words reported for immediate recall. Based on a power of 80 percent, a significance level of 0.05 and a standard deviation of 7.8, 136 participants were required to detect a difference of 5 words in immediate recall. Expecting a 25 percent dropout rate, we intended to include 170 participants.

Data analysis

Since there appeared to be little biological explanation for a possible interaction between aerobic exercise and vitamin B supplementation, the RCT was not powered to examine such an interaction effect. Consequently, both interventions were considered to be independent and results are reported for active versus placebo groups for both interventions.[22]

Differences in baseline characteristics between groups were tested using independent t-tests, Mann Whitney U tests and chi-square tests. Data were analysed according to a modified intention-to-treat analysis, including participants with at least one post-baseline assessment, using longitudinal regression analysis. The two follow-up measurements were defined as dependent variable and multi-level analysis with two levels was used, 1) time of follow-up measurement (values corresponding with performance after six and 12 months intervention); 2) individual. Reported regression coefficients indicate between-group differences. Data were analysed using a crude and an adjusted model. In the crude model, independent variables were exercise intervention, vitamin intervention and baseline performance. In the adjusted model, education, baseline physical activity level, baseline vitamin status, adherence to the exercise program and compliance with the supplementation were added as covariates. Two interaction terms were checked separately: 1) gender and interventions, and 2) exercise session attendance and interventions. Because interaction with gender was present in four of seven outcome measures, post-hoc stratification by gender was performed for all outcomes. Finally, main effects of the WP were examined according to a per protocol analysis, including all participants who attended at least 75 percent of the exercise sessions. Data were analysed using SPSS (release 12.0.2). A significance level of five percent was used for between-group comparisons and of ten percent for interaction terms.

RESULTS

Participant flow and characteristics

After baseline measurement, 179 participants were randomised to the interventions. Twenty-seven of them were excluded from the analysis, because they only provided baseline data (Figure 1). A higher percentage of these 27 participants, compared with the remaining 152 participants, was married (71 versus 52 percent, p= 0.05), and a lower percentage was a current smoker (0 versus 14 percent, p= 0.04). There were no significant differences between measures of cognition at baseline. Baseline variables for men and women who are included in the analysis, are described in Tables 2a and 2b. In the FA/B12/B6 group, a higher percentage of men was lower educated and a higher percentage of women was intermediate to high educated compared with the placebo group.

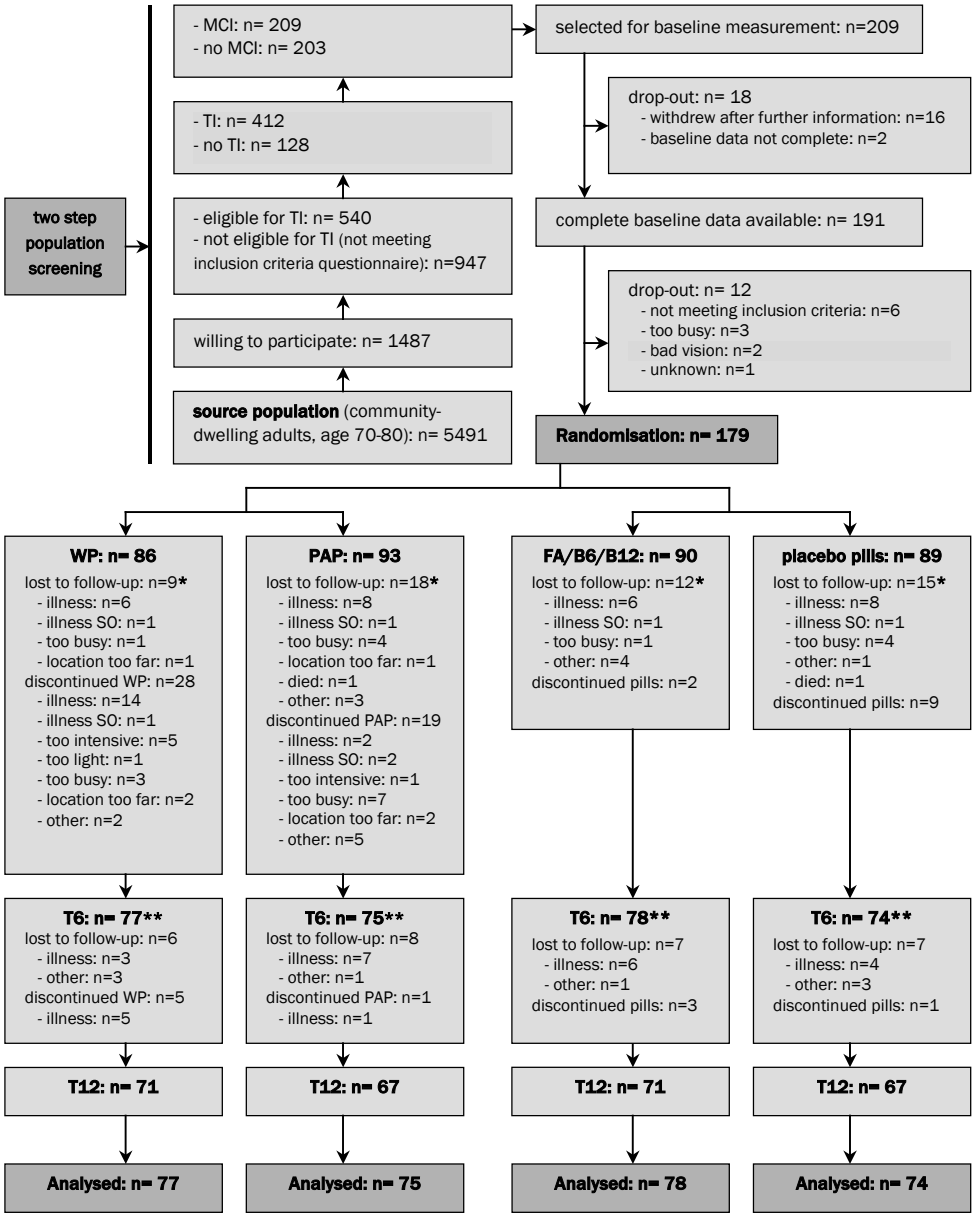

FIGURE 1: Flow chart

TI= Telephone Interview; MCI= Mild Cognitive Impairment; WP= Walking Program; PAP= Placebo Activity Program; FA/B12/B6= Folic Acid, vitamins B12 and B6; SO= Significant Other; T6= Follow-up after 6 months; T12= Follow-up after 12 months; * Excluded from analysis (only baseline data); ** Included in analysis

TABLES 2a and 2b: Baseline characteristics of male (n= 85) and female participants (n= 67)

2a: Male participants	Exercise intervention		Vitamin intervention	
	WP (n= 37)	PAP (n= 48)	FA/B12/B6 (n= 44)	Placebo (n= 41)
Age (Mean (SD))	74 (2.7)	75 (2.8)	75 (2.7)	74 (2.9)
MMSE (Median (25th; 75th ‰))	29 (28; 29)	29 (28; 29)	28 (28; 29)	29 (28; 29)
Education (% low/intermediate/high)[a]	57/ 16/ 27	42/ 35/ 23	61/ 21/ 18*	34/ 34/ 32
Marital status (% living with partner)	87	85	82	90
PA, min/day (Median (25th; 75th ‰))[b]	79 (63; 137)	79 (36; 124)	77 (55; 125)	81 (35; 125)
Vitamin status (% deficient FA/B12/B6)[c]	35/ 5/ 0	42/ 6/ 0	39/ 7/ 0	39 / 5/ 0
Hcy (% hyperhomocysteinemia)[d]	27	33	32	29
Blood pressure (% hypertension)[e]	19	32	30	22
BMI, kg/m2 (Mean (SD))	26.5 (3.4)	26.9 (3.1)	27 (3.4)	26.5 (3.0)
Smoking (% smokers)	11	15	18	7

2b: Female participants	Exercise intervention		Vitamin intervention	
	WP (n= 40)	PAP (n= 27)	FA/B12/B6 (n= 34)	Placebo (n= 33)
Age (Mean (SD))	76 (2.9)	75 (2.9)	76 (2.9)	76 (2.9)
MMSE (Median (25th; 75th ‰))	29 (28; 29)	29 (28; 30)	29 (29; 30)	29 (28; 30)
Education (% low/intermediate/high)[a]	64/28/8	70/ 19/ 11	52/ 33/ 15*	82/ 15/ 3
Marital status (% living with partner)	50	56	53	52
PA, min/day (Median (25th; 75th ‰))[b]	53 (42; 80)	48 (33; 110)	55 (41; 89)	51 (33; 80)
Vitamin status (% deficient FA/B12/B6)[c]	55/ 10/ 0	59/ 11/ 0	62/ 12/ 0	52/ 9/ 0
Hcy (% hyperhomocysteinemia)[d]	20	15	21	15
Blood pressure (% hypertension)[e]	8	19	18	7
BMI, kg/m2 (Mean (SD))	26.7 (3.0)	28.3 (4.0)	27.5 (3.9)	27.5 (3.0)
Smoking (% smokers)	15	15	15	16

WP= Walking Program; PAP= Placebo Activity Program; FA/B12/B6= Folic Acid, vitamins B12 and B6; MMSE= Mini Mental State Examination; PA= Physical Activity; Hcy= Homocysteine; BMI= Body Mass Index; [a] *low*= no education, primary education, lower vocational training, *intermediate*= intermediate level secondary education, intermediate vocational training, *high*= higher level secondary education, higher vocational training, university training; [b] ≥ 3.0 Metabolic Equivalents; [c] Cut-off points: FA red blood cell < 305 nmol/L or FA plasma < 6,3 nmol/L, B12 ≤ 150 pmol/L, B6 < 20 nmol/L; [d] Homocysteine > 14 mmol/L; [e] Hypertension= diastole ≥ 90 and systole ≥ 160; * Significantly different from placebo ($p < 0.05$)

Adherence and compliance

Thirty participants, 19 men and 11 women, did not attend a single session but were included in the intention-to-treat analysis. Median adherence (25th; 75th percentile) to both exercise programs, including these participants, was 63 (2; 81) percent and did not differ between groups. At baseline, adherent men attending at least 75 percent of the sessions (n= 33) were more often living with a partner (82% versus 65%, p= 0.03) and reported to be less physically active than non-adherent men (n= 52), (median [25th; 75th percentile] was 64 [32; 82] versus 87 [34; 139] minutes/day, p= 0.04). Most frequent reasons for drop-out from the exercise programs were health-related problems. No adverse events of the WP or PAP were reported.

Median compliance (25th; 75th percentile) with the (vitamin) supplementation was 100 (99; 100) percent. Four participants did not return the blister packs. Two participants stopped taking vitamin pills after reporting adverse sides effects, i.e. sleep problems and increased forgetfulness; one participant discontinued the placebo-pills after reporting not feeling well.

Intention-to-treat analysis

Cognitive performance at baseline and after six and 12 months intervention are presented in Tables 3a + 3b for men and in Tables 4a + 4b for women. In the intention-to-treat analysis, no significant main effect of walking or vitamin supplementation was found in men (Table 5a). In women, a beneficial main intervention effect of FA/B12/B6 was found on the DSST (beta [95%CI]= 2.9 [0.6; 5.3] symbols, p= 0.02), (Table 5b). Moreover, in women, an interaction was observed between the WP and adherence to the WP. With each percentage increase in session attendance, the SCWT-A combination task performance improved by 0.3 seconds (p= 0.04), and the AVLT delayed recall score improved by 0.04 words (p= 0.06).

TABLES 3a and 3b: Cognitive test performance at baseline and after six and 12 months in male participants (means (SD)) - WP versus PAP and FA/B12/B6 versus placebo

3a	WP			PAP		
	T0 (n= 37)	T6 (n= 37)	T12 (n= 36)	T0 (n= 48)	T6 (n= 48)	T12 (n= 45)
MMSE[a]	29 (28; 29)	28 (28; 29)	28 (27; 29)	29 (28; 29)	28 (27; 29)	28 (28; 29)
AVLT 1-5 (words)	32.7 (7.8)	33.7 (10.8)	30.1 (9.4)	30.4 (6.9)	33.2 (9.1)	30.3 (9.0)
AVLT 6 (words)	5.9 (2.5)	6.2 (3.0)	5.1 (2.9)	5.3 (2.3)	6.3 (3.1)	4.7 (2.6)
SCWT-A task 1[b] (s)	19.1 (3.8)	19.3 (4.3)	20.1 (4.7)	19.3 (3.6)	19.3 (4.6)	18.8 (3.9)
SCWT-A task 2[b] (s)	25.4 (4.2)	25.1 (5.1)	25.0 (4.8)	25.3 4.9)	25.6 (5.6)	26.1 (5.3)
SCWT-A task 3[b] (s)	60.5 (20.0)	65.4 (25.7)	57.9 (14.0)	59.0 (18.8)	62.1 (30.9)	58.4 (22.1)
DSST (symbols)	35.5 (10.7)	36.4 (10.4)	35.5 (10.0)	38.6 (10.0)	38.8 (9.5)	38.4 (11.3)
VFT (words)	30.4 (9.9)	31.7 (8.9)	32.6 (8.0)	30.3 (11.0)	33.5 (12.3)	34.7 (14.2)

3b	FA/B12/B6			Placebo		
	T0 (n= 44)	T6 (n= 44)	T12 (n= 43)	T0 (n= 41)	T6 (n= 41)	T12 (n= 38)
MMSE[a]	28 (28; 29)	28 (27; 29)	28 (27; 30)	29 (28; 29)	28 (28; 29)	29 (28; 29)
AVLT 1-5 (words)	31.1 (7.5)	31.3 (9.8)	29.1 (8.9)	31.7 (7.2)	35.8 (9.4)	31.5 (9.3)
AVLT 6 (words)	5.6 (2.7)	5.9 (3.2)	4.9 (2.9)	5.5 (2.1)	6.6 (2.8)	5.2 (2.5)
SCWT-A task 1[b] (s)	19.6 (3.7)	19.7 (4.3)	19.5 (4.5)	18.9 (3.7)	18.9 (4.6)	19.2 (4.1)
SCWT-A task 2[b] (s)	25.8 (4.1)	26.1 (4.4)	25.8 (4.4)	24.9 (5.1)	24.7 (6.3)	25.4 (5.8)
SCWT-A task 3[b] (s)	62.6 (21.1)	65.5 (29.9)	61.0 (22.4)	56.4 (16.6)	61.4 (27.5)	54.8 (12.8)
DSST (symbols)	36.2 (11.7)	35.7 (10.2)	36.2 (12.1)	38.3 (8.7)	39.9 (9.2)	38.1 (9.1)
VFT (words)	28.3 (10.7)	31.2 (11.2)	31.8 (10.3)	32.5 (9.9)	34.3 (10.6)	36.0 (13.3)

WP= Walking Program; PAP= Placebo Activity Program; FA/B12/B6= Folic Acid, vitamin B12 and B6; AVLT= Auditory Verbal Learning Test; SCWT-A= Stroop Colour Word Test- Abridged; s= Seconds; DSST= Digit Symbol Substitution Test; VFT= Verbal Fluency Test; [a] Median (25th; 75th percentiles); [b] Lower score indicates better performance

TABLES 4a and 4b: Cognitive test performance at baseline and after six and 12 months in female participants (means (SD)) - WP versus PAP and FA/B12/B6 versus placebo

4a	WP			PAP		
	T0 (n= 40)	T6 (n= 40)	T12 (n= 35)	T0 (n= 27)	T6 (n= 27)	T12 (n= 22)
MMSE[a]	29 (28; 29)	28 (28; 29)	29 (27; 29)	29 (28; 30)	29 (27; 30)	29 (27; 30)
AVLT 1-5 (words)	34.6 (8.2)	34.2 (11.1)	32.1 (9.0)	34.3 (8.3)	34.7 (7.6)	33.0 (7.7)
AVLT 6 (words)	6.3 (2.6)	6.2 (3.6)	5.6 (3.0)	6.0 (2.3)	6.5 (3.1)	5.5 (2.7)
SCWT-A task 1[b] (s)	21.1 (5.8)	20.6 (5.4)	19.9 (4.7)	20.2 (3.5)	20.4 (4.3)	21.4 (4.2)
SCWT-A task 2[b] (s)	26.5 (5.7)	26.9 (6.1)	25.4 (5.3)	26.0 (5.1)	24.7 (4.8)	25.4 (4.1)
SCWT-A task 3[b] (s)	63.2 (22.1)	64.7 (24.4)	60.7 (25.3)	65.6 (20.0)	71.2 (33.4)	65.2 (24.8)
DSST (symbols)	34.7 (9.7)	35.0 (9.9)	35.5 (9.6)	35.5 (10.5)	35.2 (12.6)	34.4 (8.6)
VFT (words)	29.7 (9.2)	30.6 (8.2)	36.1 (11.3)	27.7 (8.6)	31.4 (9.3)	33.8 (11.0)

4b	FA/B12/B6			Placebo		
	T0 (n= 34)	T6 (n= 34)	T12 (n= 28)	T0 (n= 33)	T6 (n= 33)	T12 (n= 29)
MMSE[a]	29 (28; 30)	29 (28; 30)	29 (27; 30)	29 (28; 30)	28 (27; 29)	29 (27; 30)
AVLT 1-5 (words)	34.9 (8.9)	35.1 (10.8)	33.7 (10.0)	34.1 (7.4)	33.7 (8.8)	31.2 (6.6)
AVLT 6 (words)	6.4 (2.4)	6.8 (3.6)	5.7 (3.0)	6.0 (2.5)	5.9 (3.1)	5.4 (2.8)
SCWT-A task 1[b] (s)	20.1 (5.3)	19.8 (5.2)	20.2 (4.3)	21.4 (4.6)	21.3 (4.6)	20.8 (4.8)
SCWT-A task 2[b] (s)	25.3 (6.2)	25.0 (5.7)	25.0 (5.2)	27.0 (4.6)	27.0 (5.6)	25.6 (4.6)
SCWT-A task 3[b] (s)	60.2 (18.1)	62.6 (25.0)	60.7 (26.3)	68.4 (23.5)	72.2 (30.1)	64.1 (24.1)
DSST (symbols)	36.4 (10.9)	37.7 (11.6)	36.6 (10.3)	33.7 (8.9)	32.5 (10.0)	33.5 (7.7)
VFT (words)	28.9 (9.2)	31.2 (8.2)	33.8 (10.1)	29.0 (8.9)	30.6 (9.2)	36.7 (12.1)

WP= Walking Program; PAP= Placebo Activity Program; FA/B12/B6= Folic Acid, vitamin B12 and B6; AVLT= Auditory Verbal Learning Test; SCWT-A= Stroop Colour Word Test- Abridged; s= Seconds; DSST= Digit Symbol Substitution Test; VFT= Verbal Fluency Test; [a] Median (25th; 75th percentiles); [b] Lower score indicates better performance

Per protocol analysis

Per protocol analysis was performed in men attending at least 75 percent of the sessions (n= 33). A beneficial effect of the WP on AVLT delayed recall was observed (beta [95%CI]= 1.5 [0.1; 3.0] words, p= 0.04). Since only 18 women attended at least 75 percent of the sessions, it was not possible to perform reliable per protocol analysis in women.

TABLES 5a and 5b: The effects of the WP and FA/B6/B12 supplementation on change in cognitive performance in male and female participants (adjusted model)

5a: Male participants	WP (n= 37) vs. PAP (n= 48) Beta (95%CI)	p-value	FA/B12/B6 (n= 44) vs. placebo (n= 41) Beta (95%CI)	p-value
AVLT 1-5 (words)	-1.4 (-4.1; 1.3)	0.31	-2.2 (-5.1; 0.6)	0.12
AVLT 6 (words)	-0.2 (-1.0; 0.6)	0.58	-0.5 (-1.3; 0.3)	0.25
SCWT-A task 1[a] (s)	0.6 (-0.6; 1.8)	0.29	0.0 (-1.3; 1.2)	0.98
SCWT-A task 2[a] (s)	-1.0 (-2.2; 0.2)	0.10	0.1 (-1.1; 1.4)	0.84
SCWT-A task 3[a] (s)	0.9 (-6.8; 8.7)	0.81	3.1 (-5.1; 11.3)	0.45
DSST (symbols)	0.9 (-1.2; 3.0)	0.40	-1.4 (-3.7; 0.8)	0.20
VFT (words)	-1.7 (-4.4; 1.0)	0.21	0.8 (-2.0; 3.6)	0.58
AVLT 1-5 (words)	-1.4 (-4.1; 1.3)	0.31	-2.2 (-5.1; 0.6)	0.12
AVLT 6 (words)	-0.2 (-1.0; 0.6)	0.58	-0.5 (-1.3; 0.3)	0.25

5b: Female participants	WP (n= 40) vs. PAP (n= 27) Beta (95%CI)	p-value	FA/B12/B6 (n= 34) vs. placebo (n= 33) Beta (95%CI)	p-value
AVLT 1-5 (words)	-0.6 (-3.8; 2.6)	0.72	-0.1 (-3.4; 3.3)	0.97
AVLT 6 (words)	-0.4 (-1.6; 0.9)	0.56	0.0 (-1.3; 1.3)	0.99
SCWT-A task 1[a] (s)	-1.3 (-2.9; 0.3)	0.10	-0.9 (-2.6; 0.7)	0.27
SCWT-A task 2[a] (s)	0.6 (-0.9; 2.1)	0.46	-0.7 (-2.2; 0.9)	0.39
SCWT-A task 3[a] (s)	-4.1 (-13.3; 5.2)	0.38	-1.1 (-10.8; 8.7)	0.83
DSST (symbols)	0.8 (-1.4; 3.1)	0.47	2.9 (0.6; 5.3)	0.02
VFT (words)	-1.4 (-4.8; 2.0)	0.42	-1.0 (-4.5; 2.6)	0.59
AVLT 1-5 (words)	-0.6 (-3.8; 2.6)	0.72	-0.1 (-3.4; 3.3)	0.97
AVLT 6 (words)	-0.4 (-1.6; 0.9)	0.56	0.0 (-1.3; 1.3)	0.99

WP= Walking Program; PAP = Placebo Activity Program; FA/B12/B6= Folic Acid, vitamins B12 and B6; AVLT= Auditory Verbal Learning Test; SCWT-A= Stroop Colour Word Test- Abridged; s= Seconds; DSST= Digit Symbol Substitution Test; VFT= Verbal Fluency Test; [a] Lower score indicates better performance

DISCUSSION

The walking program and/or FA/B12/B6 supplementation were not effective at improving cognition in community-dwelling older adults with MCI within one year. The walking program, however, was efficacious in improving memory in men and memory and complex processing in women with sufficient adherence.

To our knowledge, this is the first intervention study targeting subjects with MCI from the general population. The effect of walking in frail institutionalised subjects with MCI (n= 43, mean age 86 years) has been examined.[37] However, the study population and

characteristics of the walking program differed considerably from those of our study. Although subjects with MCI have an increased risk of developing Alzheimer's disease, it is possible to revert to normal cognitive function without intervening.[38] By including participants with MCI, the expected benefits of the WP and FA/B6/B12 supplementation may have been overshadowed because of the natural fluctuating course of MCI. Furthermore, with respect to conversion rates[2], longer interventions would have been needed for significant preventive effects on cognitive decline.

In the present study, a benefit of FA/B12/B6 supplementation was only observed on complex processing in women. This is in line with the conclusions of recent meta-analyses, that published trials do not yet provide adequate evidence for an effect of supplementation with folic acid, vitamins B12 and B6, alone or in combination, on tests for cognitive function in people with normal or impaired cognitive function.[18-20,39] A possible explanation for the lack of effect in our study may be the absence of screening for baseline vitamin deficiencies or hyperhomocysteinemia. However, there also was no main intervention effect on cognition in a post-hoc subgroup analysis of participants with baseline folate deficiency and/or hyperhomocysteinemia (n= 85, data not shown). A higher dose of vitamin B supplementation seems not a good option, since FA/B12/B6 supplementation significantly improved homocysteine and vitamin B concentrations within six months (Chapter 5.4). However, these changes did not result in a measurable improvement in cognitive function. Furthermore, a very high dose was already given and the benefit of lowering homocysteine concentrations by vitamin B supplementation is currently in question.[40] However, it is possible that a longer duration of vitamin B supplementation is necessary to promote cognitive function. In contrast to relatively short-term interventions, Durga et al. (2007) observed a beneficial effect on cognitive performance in subjects with increased homocysteine and normal vitamin B12 concentrations at baseline, after three years of supplementation with 800 micrograms of folic acid.[41]

In the intention-to-treat analysis, no main effect of the walking program on cognition was found. These results do not correspond to two recent meta-analyses on the effects of physical activity and exercise on cognitive function in cognitively healthy and demented subjects, which found significant positive effect sizes.[7,8] Colcombe et al. (2003) included 18 intervention studies describing the effect of supervised exercise programs with an aerobic component. Most trials were executed in community-dwelling, cognitively healthy, but sedentary subjects in whom larger effects of exercise on cognition can be expected.[7] In the present study, no selection was made on the basis of baseline physical activity level. Heyn et al. (2004), included 12 randomised trials that examined the effect of any exercise or

physical activity program on cognitive function in demented subjects. Mean MMSE-scores in included subjects ranged from 6 to 25, compared with a mean MMSE-score of 29 in the present study. For both meta-analyses, the possibility cannot be excluded that the conclusions were influenced by publication bias.

First, the lack of a main intervention effect in the present study may have been caused by the moderate adherence to the exercise programs. Many previous studies only included subjects who completed the program (Chapter 2). A strength of the present study is that data were analysed according to the intention-to-treat principle, including all randomised participants with available data, irrespective of compliance with the study protocol. As a result, a considerable number of participants (30 out of 152) who did not attend a single exercise session was included in the intention-to-treat analysis. This may have underestimated the actual intervention effect. In contrast, adherence could have affected the results of the per protocol analysis in the opposite direction. If only participants without progressive MCI were able to adhere to the walking program, this may have been responsible for the positive effects instead of the walking program itself. However, the correlation between baseline MMSE-score and adherence was small (spearman r= 0.14) and not significant. Moreover, adherent and non-adherent participants did not differ significantly with respect to cognitive status at baseline, six and 12 months, according to MMSE-scores.

Secondly, larger effects of exercise on cognition are expected in sedentary subjects.[7] Therefore, the lack of main effects may be explained by the relatively high self-reported physical activity levels at baseline. Around 80 percent of the women and 90 percent of the men reported to be at least moderate intensity physically active for 30 minutes or more per day. In comparison, in the general Dutch population 65 to 75 years of age, only 60 percent of women and 70 percent of men can make this claim.[42] Nevertheless, despite high baseline activity levels, the WP was efficacious in improving aerobic fitness compared with the PAP (Chapter 5.3). It is possible that a threshold physical activity level exists, above which additional moderate-intensity physical activity does not result in further cognitive benefit.

Third, it is possible that the contrast between both programs was not large enough to induce between group differences. However, according to heart rate recordings during the exercise sessions, intensity of the WP commensurated with moderate intensity and intensity of the PAP with very low intensity (Chapter 5.3). Furthermore, the use of a low-intensity

placebo activity program with non-aerobic exercise in the present study is a strength, which offers the opportunity to exclude the Hawthorne effect of attention.
Finally, our results may be explained by the strong methodological design of the study. Etnier et al. (1997) performed a thorough meta-analysis on the effect of exercise on cognition.[43] In subjects 60 to 90 years of age, a small positive effect size was observed. However, they found that the effect size decreased as experimental rigor increased. The rigorous design of our study, which included intention-to-treat analysis, participants, exercise instructors and outcome assessors being blinded to group allocation, and a range of valid measurements assessing cognition, reduces the likelihood that bias affected our results.

To conclude, our results do not support the suitability of vitamin B supplementation for improving cognitive function. However, our findings suggest that regular participation in moderate-intensity walking may improve cognitive function, especially memory, in community dwelling people with MCI. Therefore, irrespective of cognitive status, regular participation in moderate-intensity physical activity should be encouraged. Future studies are needed to confirm our findings and to examine ways to increase exercise frequency among this population.

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5.2

The effect of walking and vitamin B supplementation on quality of life in community-dwelling older adults with mild cognitive impairment

JGZ van Uffelen, MJM Chin A Paw, M Hopman-Rock, W van Mechelen
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ABSTRACT

Objectives

To examine the effect of walking and vitamin B supplementation on quality-of-life (QoL) in community-dwelling adults with mild cognitive impairment

Methods

One year, double-blind, placebo-controlled trial. Participants were randomised to: 1) twice-weekly, group-based, moderate-intensity walking program (n= 77) or a low-intensity placebo activity program (n= 75); and 2) daily vitamin B pills containing 5 mg folic acid, 0.4 mg B12, 50 mg B6 (n= 78) or placebo pills (n= 74). QoL was measured at baseline, after six and 12 months using the population-specific Dementia Quality-of-Life (D-QoL) to assess overall QoL and the generic Short-Form 12 mental and physical component scales (SF12-MCS and SF12-PCS) to assess health-related QoL.

Results

Baseline levels of QoL were relatively high. Modified intention-to-treat analysis revealed no positive main intervention effect of walking or vitamin supplementation. In both men and women, ratings of D-QoL-belonging and D-QoL-positive affect subscales improved by 0.003 (p= 0.04) and 0.002 points (p= 0.06) with each percent increase in attendance at the walking program. Only in men, SF12-MCS increased by 0.03 points with each percent increase in attendance (p= 0.08).

Conclusion

Several small but significant improvements in QoL were observed with increasing attendance at the walking program. No effect of vitamin B supplementation was observed.

INTRODUCTION

Especially in older people, both mental and physical function decrease due to multiple age-related changes, which in turn may affect quality of life (QoL). The most obvious decrease in mental function is cognitive decline, which is a common aspect of ageing. However, in some cases decline is more serious than expected for a certain age. This is specified as Mild Cognitive Impairment (MCI). MCI is considered to be a potential transitional stage between normal cognitive function and Alzheimer's disease, characterised by: 1) subjective memory complaints; 2) objective memory impairment; 3) normal mental status; 4) intact activities of daily living (ADL); and 5) absence of dementia.[1] Independent of the latter four criteria, subjective memory complaints are related to lower QoL.[2] Moreover, MCI is associated with poor physical health and high risk of ADL dependence.[3,4] Since both cognitive and physical decline belong to the most important determinants of QoL in community-dwelling elderly people[5], subjects with MCI are likely to be susceptible to a decrease in QoL.

The number of adults with MCI is increasing considerably due to the ageing population. For multiple reasons, it is important to prevent a decrease in QoL. Apart from the personal benefits, a high rated QoL also reduces medical consumption and helps to maintain independency as long as possible.[6] This in turn may relieve significant others, caregivers and medical society in general. For this reason, attention should be paid to possible interventions contributing towards a higher level of overall QoL and it's mental and physical components. In this respect, physical exercise and vitamin supplementation are interesting interventions worth investigating. Regular participation in moderate intensity aerobic training is reported to be beneficial in improving QoL and wellbeing, which is an important aspect of QoL.[7,8] Since walking is the most prevalent physical activity among older adults[9], improving QoL by increasing the time spent on moderate intensity walking seems promising. Indeed, a community-based walking program significantly improved both the physical and mental components of health-related QoL in older adults (n= 582).[10] Inconclusive evidence has been reported on the influence of vitamin B supplementation on QoL. Different aspects of QoL were not responsive to short term supplementation (range 4 to 12 weeks) with different doses and combinations of B vitamins in men and women.[11-13]

Not much is known about QoL in community dwelling elderly people with MCI. Moreover, no trials on the effect of exercise and vitamin B supplementation on QoL have been carried out yet in adults with MCI. The FACT-study (Folate physical Activity Cognition Trial) was developed to examine the effect of these interventions on cognition.[14] Aspects of QoL were measured as a secondary outcome. In the present paper, the effectiveness of one year of

moderate intensity walking (two sessions of 60 minutes per week) and daily vitamin B supplementation (5 mg folate, 50 mg vitamin B6 and 0.4 mg B12) on both overall QoL and its health-related components is examined in community dwelling older adults with MCI. We hypothesise that one year of moderate intensity walking benefits QoL. Concerning the effect of vitamin supplementation, this paper should be considered as explorative.

METHODS

Study design

The study was designed as a randomised, placebo-controlled intervention trial, based on a two-by-two factorial design. The study-protocol has been described in detail elsewhere[14], and was approved by the VU University Medical Center medical ethics committee. Written informed consent was obtained from all participants.

Participants

In a medium-sized Dutch town community-dwelling subjects aged 70 to 80 years with MCI were identified using a population-based two-step-screening.[15] The operational criteria for MCI according to the criteria of Petersen et al.[1] and additional inclusion criteria for the RCT are described in Table 1. Subjects were not paid to participate in the study.

Randomisation

After the baseline interview, participants were randomly assigned to the interventions using the statistical computer program SPSS. Intervention groups were: 1) walking program or placebo activity program; and 2) vitamin B supplementation or placebo supplementation. Randomisation was stratified for physical activity level at baseline in minutes per day as measured by the LASA physical activity questionnaire.[16] For the flow of participants see Figure 1.

TABLE 1: Inclusion and exclusion criteria for participation in the trial

Operationalisation of Petersen criteria for MCI (1-5) and additional inclusion criteria for the RCT (6-12)
1. Memory complaints (answer yes to question 'do you have memory complaints', or at least twice sometimes at cognition scale of Strawbridge[17])
2. Objective memory impairment; 10 WLT[18] delayed recall ≤ 5 + percentage savings ≤ 100
3. Normal general cognitive functioning; TICS[19] ≥ 19 + MMSE[20] ≥ 24
4. Intact daily functioning: no report of disability in activities of daily living on GARS-scale[21], except on the item 'taking care of feet and toe nails'
5. Absence of dementia; TICS ≥ 19 + MMSE ≥ 24
6. Being able to perform moderate intensity physical activity, without making use of walking devices, e.g. a rollator or a walking frame
7. Not using vitamin supplements/ vitamin injections/ drinks with dose of folic acid, vitamins B12 or B6 comparable to vitamin supplement given in intervention
8. Not suffering from epilepsy, multiple sclerosis, Parkinson's disease, kidney disorder requiring haemodialysis, psychiatric impairment
9. Not suffering from depression as measured by the GDS[22] (cut-off ≤ 5)
10. Not using medication for rheumatoid arthritis or psoriasis interfering with vitamin supplement
11. No alcohol abuse (men < 21 consumptions a week, women < 15 consumptions a week)
12. Not currently living in a nursing home or on a waiting list for a nursing home

MCI= Mild Cognitive Impairment; RCT= Randomised Controlled Trial; 10 WLT= 10 Word Learning Test; TICS= Telephone Interview for Cognitive Status; MMSE= Mini Mental State Examination; GARS= Groningen Activity Restriction Scale; GDS= Geriatric Depression Scale

Exercise intervention

Participants assigned to the walking program (WP) participated twice a week for 60 minutes in group-based moderate intensity walking during one year. Each session consisted of a warm-up, moderate intensity walking exercises and a cool-down. The WP was based on 'Sportive Walking', an existing aerobic walking program[23] designed to improve aerobic fitness. Therefore, duration and intensity of the walking exercises increased gradually during the program. Sessions took place outdoors in municipal parks. Participants not assigned to the WP, participated in a placebo activity program (PAP) with the same frequency, session duration and program duration. However, the PAP consisted of low intensity exercise, such as range of motion movements and stretching. Sessions were divided into five themes: relaxation, activities of daily living, balance, flexibility, posture and a combination of all. For each theme three sessions were developed and the entire series of 18 sessions was repeated during the intervention period. The PAP was carried out in community centres. Both programs were supervised by qualified and trained instructors. Attendance at both programs was assessed by the percentage of attended sessions.

Vitamin supplementation (FA/B12/B6)

Participants in the vitamin supplementation group took one pill containing 5 mg vitamin B11 (Folic Acid), 0.4 mg vitamin B12 (Cyanocobalamin) and 50 mg vitamin B6 (Pyridoxine-hydrochloride) daily during one year. This vitamin supplement is available on prescription in The Netherlands. Participants randomised to the control group took an identically looking placebo pill. The pills were packed in blister packs for one week, which were labelled for each day of the week. Compliance with the vitamin supplementation was verified by pill counts in returned blister packs during the intervention.

Outcome measures

Baseline data on sociodemographic and background variables were collected using a postal screening questionnaire. The measurement of other baseline variables, as reported in Table 2, has been described elsewhere.[14] In the present paper, a distinction was made between 'overall quality of life', referring to a subjects overall enjoyment of life and 'health-related quality of life', referring to health- related factors affecting quality of life. The term QoL was used as an umbrella term for both overall and health-related QoL. The population-specific Dementia Quality of Life questionnaire (D-QoL)[24] was used to assess overall QoL and the generic Short Form 12 (SF12)[25] to assess health-related QoL. The D-QoL is a 29 item measure especially developed for subjects with cognitive decline and dementia. The participant is asked about how much they enjoyed activities that were reported to be important for elderly people, such as 'watching animals'. Moreover, participants were asked about the frequency of certain positive and negative feelings such as 'lovable' or 'worried'. Finally, they were asked to rate their overall quality of life. The participant was instructed to choose the best fitting answer from five item response scales. The answers were divided into five domains of QoL measuring sense of aesthetics, feelings of belonging, negative affect, positive affect/ humour and self esteem. A mean score ranging from one to five was calculated for these subscales and for the total D-QoL. A higher score indicated better quality of life. Median internal consistency reliability of the D-QoL was 0.80 and median test-retest reliability was 0.72 in a sample of 95 older adults with different stages of cognitive decline.[24] The SF12 consists of twelve items measuring eight concepts of both mental and physical health, i.e. physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role emotional and mental health. These concepts are summarised as two scores using a norm-based criterion: i.e. mental and physical component summary scales (SF12-MCS and SF12-PCS). The mean score is 50 with a standard deviation of ten. For example, a score of 60 corresponds to a QoL rating of one standard deviation above the average ratings in the general population. Test retest reliability for the SF-12 MCS was 0.76

in a sample of 187 adults in the United Kingdom and 0.77 in a sample of 232 adults in the United States. Reliability coefficients of the SF-12 PCS in these populations were 0.86 and 0.89 respectively.[25] In the present study, measurement took place during a personal interview at baseline and after six and 12 months. Both the D-QoL and the SF-12 were administered by a trained interviewer who was unaware of the participants' group allocation.

Statistical analysis

Differences between groups in baseline characteristics were tested using independent t-tests (normally distributed variables), Mann Whitney U tests (not normally distributed variables) and chi-square tests (categorical variables). Within group differences were tested using dependent t-tests.

Subsequently, data were analysed according to a modified intention-to-treat principle, based on data from all randomised participants who provided data at baseline and at least one follow-up measurement. To evaluate the effects of the walking program and the vitamin supplementation on QoL, longitudinal regression analysis was used. The two follow-up measurements were defined as dependent variable and multi level analysis with two levels was used, 1) time of follow-up measurement (values corresponding with performance after six and 12 months intervention); 2) individual. According to the study protocol[14], the effect of both interventions was examined independently from each other. Data were analysed using a crude and an adjusted model. Independent variables were exercise intervention and vitamin intervention. By analysing both interventions in the same model, results were adjusted for the possible influence of the other intervention. Moreover, all analyses were adjusted for baseline performance on the outcome measure by adding this as a covariate. In the adjusted model, education, baseline physical activity level, baseline vitamin status, attendance at the exercise program and compliance with the supplementation were added as covariates. Interaction between gender and the WP or FA/B6/B12-supplementation was checked in the adjusted model. In the case of significant interaction, results were reported for men and women separately. In the case of no interaction, gender was added to the adjusted model as an additional covariate. Also, in the 'adjusted model' an interaction effect of the exercise program and attendance at the exercise program was checked. Finally, data were analysed according to the per protocol principle, including all participants who attended at least 75 percent of the sessions. This cut-off point is in concordance with previous exercise intervention studies in older adults.[26,27]

Data were analysed using SPSS for Windows (release 12.0.1). A significance level of five percent was used for between group comparisons and of ten percent for interaction terms. Regression coefficients and 95 percent confidence intervals for the adjusted models were reported, with the regression coefficients directly indicating the difference in QoL ratings between the WP and the PAP or the FA/B12/B6-supplementation and the placebo supplementation. In the case of significant interaction, regression coefficients and the 95 percent confidence intervals of the interaction terms were reported.

RESULTS

Patient characteristics

One hundred and seventy-nine participants were randomised to the interventions. Twenty-seven of them were excluded from analysis, because they only provided baseline data. These participants were more often married (71 versus 52 percent, p= 0.05) and less often current smokers (0 versus 14 percent, p= 0.04) than the remaining 152 participants who provided QoL data at baseline and at at least one follow-up measurement. The latter 152 participants were included in the analysis (see Figure 1). Their mean age (SD) was 75 (2.9) years. Fifty-six percent were male. Additional baseline variables are described in Table 2. Compared with the PAP, the WP included fewer men (48% in WP versus 64% in PAP) and more participants with hypertension (27% in WP versus 14% in PAP). Ratings for both overall and health-related QoL at baseline and after six and twelve months intervention are presented in Tables 3a and 3b. No baseline differences were observed in these measures, except for a higher rating of D-QoL self-esteem in participants in the FA/B12/B6-group compared with participants in the placebo-supplementation group.

Attendance at the WP and the PAP

Overall median attendance at the exercise programs (10^{th}; 90^{th} percentile) was 63 (0; 89) percent and did not differ between the WP and the PAP. Especially in the first weeks, a considerable number of participants discontinued participation, mostly because they did not want to participate in the exercise programs after all. Most frequent reasons for discontinuation of the program after the first weeks were health-related problems. No adverse events of the WP or PAP itself were reported. Adherent participants attending at least 75 percent of the sessions (n= 51) were more often living with a partner (82% versus 65%, p= 0.03) and less physically active than non-adherers (n= 101), (median [10^{th}; 90^{th} percentile] was 36 [13; 82] versus 44 [10; 169] minutes/day, p= 0.02). At baseline, adherers also had lower ratings of D-QoL-belonging (3.6 [0.41] versus 3.8 [0.49], p= 0.02) and higher SF12-MCS values (56.5 [5.6] versus 53.7 [8.1], p= 0.02). Other baseline and QoL characteristics did not differ significantly.

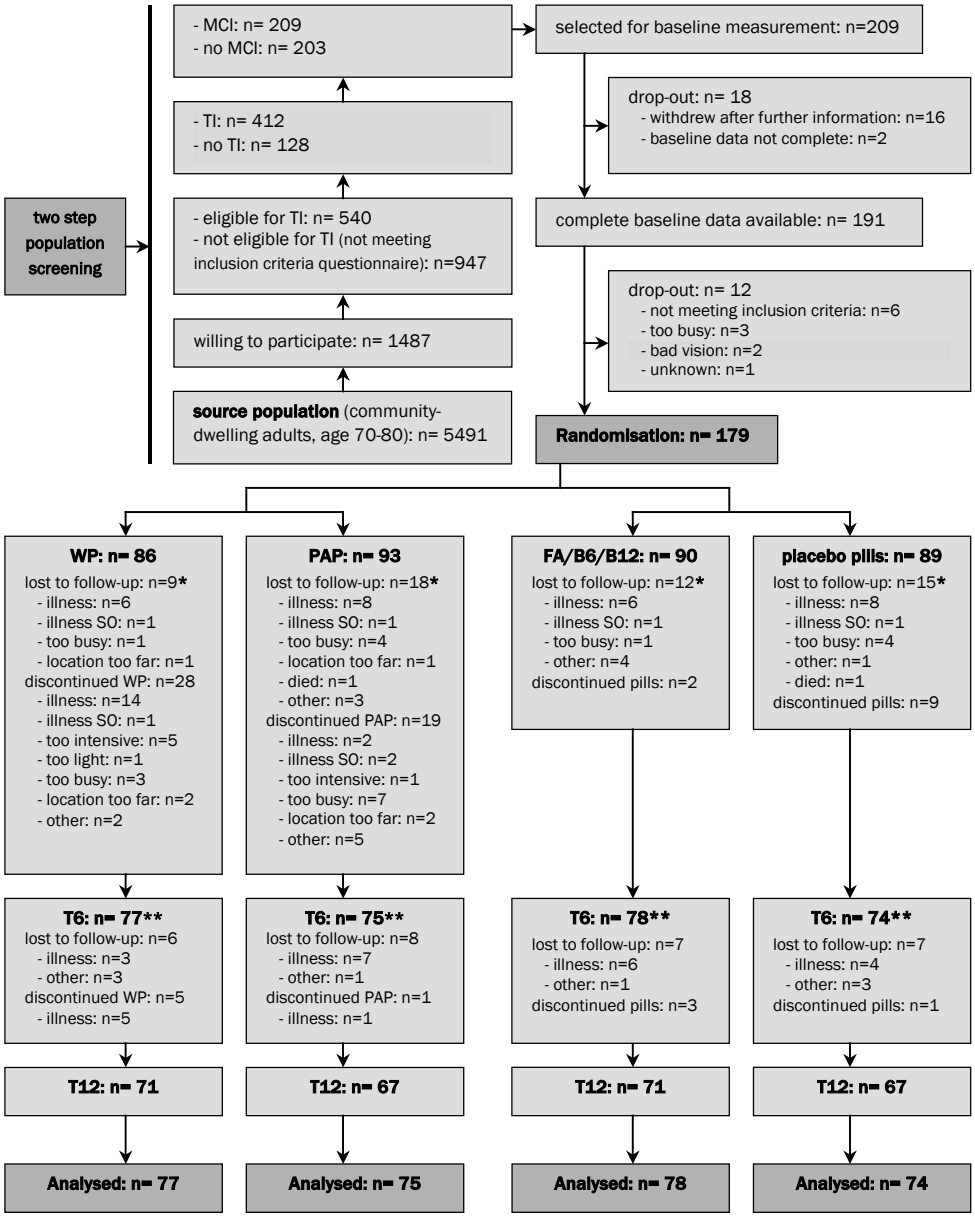

FIGURE 1: Flow chart

TI= Telephone Interview; MCI= Mild Cognitive Impairment; WP= Walking Program; PAP= Placebo Activity Program; FA/B12/B6= Folic Acid, vitamins B12 and B6; SO= Significant Other; T6= Follow-up after 6 months; T12= Follow-up after 12 months; * Excluded from analysis (only baseline data); ** Included in analysis

TABLE 2: Baseline characteristics of participants (n= 152)

	Exercise intervention		Vitamin intervention	
	WP (n= 77)	PAP (n= 75)	FA/B12/B6 (n= 78)	Placebo (n= 74)
Age (Mean (SD))	75 (2.9)	75 (2.8)	75 (2.8)	75 (2.9)
Gender (% male)	48*	64	56	55
MMSE (Median (10^{th}; 90^{th} ‰))	29 (26; 30)	29 (27; 30)	29 (25; 30)	29 (27; 30)
Education (% low/intermediate/high)[a]	61/22/17	52/29/19	57/26/17	55/26/19
Marital status (% living with partner)	75	68	69	73
PA, min/day (Median (10^{th}; 90^{th} ‰))[b]	71 (43; 88)	67 (36; 124)	72 (43; 108)	64 (33; 89)
Vitamins (% deficient FA/B12/B6)[c]	46/8/0	48/8/0	49/9/0	45/7/0
Hcy (% hyperhomocysteinemia)[d]	27	23	27	23
Blood pressure (% hypertension)[e]	27*	14	25	16
BMI, kg/m2 (Median (10^{th}; 90^{th} ‰))	26.7 (23.1; 31.5)	26.6 (23.5; 32.7)	26.5 (23.3; 32.8)	26.7 (23.5; 31.2)
Smoking (% smokers)	13	15	17	11
Self-reported diseases (% 0,1,2)[f]	52/42/6	69/27/4	66/28/6	55/41/4

WP= Walking Program; PAP= Placebo Activity Program; FA/B12/B6= Folic Acid, vitamins B12 and B6; MMSE= Mini Mental State Examination; PA= Physical Activity; Hcy= Homocysteine; BMI= Body Mass Index; [a] *low*= no education, primary education, lower vocational training, *intermediate*= intermediate level secondary education, intermediate vocational training, *high*= higher level secondary education, higher vocational training, university training; [b] ≥ 3.0 Metabolic Equivalents; [c] Cut-off points: FA red blood cell < 337 nmol/L or FA plasma < 6,3 nmol/L, B12 ≤ 150 pmol/L, B6 < 20 nmol/L; [d] Homocysteine > 14 mmol/L; [e] Hypertension= diastole ≥ 90 and systole ≥ 160; [f] Cardiovascular disease, chronic obstructive pulmonary disease, diabetes, epilepsy, multiple sclerosis, Parkinson's disease, psychiatric disease, renal failure requiring dialysis and/or rheumatoid arthritis; * Significantly different from PAP ($p < 0.05$)

Compliance with the (FA/B12/B6) supplementation

Four participants did not return the blister packs. On the basis of pill counts in returned blister packs, median compliance (10^{th}; 90^{th} percentile) with the FA/B12/B6-supplementation was 100 (97; 100) percent and compliance with placebo-supplementation was 100 (35; 100) percent. Even though median compliance in both groups was 100 percent, compliance in the placebo-group was significantly lower ($p < 0.05$). Eight participants, one in the FA/B12/B6-group and seven in the placebo-group, did not take (vitamin)supplementation. Seven of them decided immediately after randomisation not to participate in the interventions. The other wanted to participate in the exercise intervention only. Two participants discontinued taking vitamin pills during the trial after reporting sleep problems and increased forgetfulness; one participant discontinued taking the placebo pills after reporting not feeling well.

TABLES 3a and 3b: QoL ratings at baseline and after six and 12 months in older adults with MCI[a] (Means (SD)) - WP versus PAP and FA/B12/B6 versus placebo

3a	WP			PAP		
	T0 (n= 77)	T6 (n= 77)	T12 (n= 71)	T0 (n= 75)	T6 (n= 75)	T12 (n= 67)
D-QoL sumscore	3.5 (0.26)	3.5 (0.29)	3.5 (0.27)	3.5 (0.32)	3.5 (0.34)	3.5 (0.34)
D-QoL aesthetics	3.5 (0.63)	3.5 (0.64)	3.6 (0.60)	3.5 (0.70)	3.5 (0.71)	3.5 (0.65)
D-QoL belonging	3.7 (0.50)	3.7 (0.49)	3.7 (0.44)	3.8 (0.45)	3.7 (0.47)	3.7 (0.46)
D-QoL negative affect	2.7 (0.45)	2.7 (0.46)	2.8 (0.50)	2.7 (0.55)	2.8 (0.54)	2.8 (0.52)
D-QoL positive affect	3.8 (0.39)	3.7 (0.46)	3.8 (0.40)	3.8 (0.40)	3.7 (0.44)	3.8 (0.43)
D-QoL self esteem	3.6 (0.45)	3.8 (0.41)	3.8 (0.40)	3.7 (0.48)	3.7 (0.49)	3.8 (0.48)
SF12-MCS	54.6 (6.85)	55.6 (6.40)	55.3 (4.39)	54.7 (8.07)	55.0 (7.34)	55.3 (6.24)
SF12-PCS	48.2 (7.15)	48.1 (7.57)	50.5 (6.13)	48.7 (7.86)	48.8 (8.47)	49.8 (7.04)

3b	FA/B12/B6			Placebo		
	T0 (n= 78)	T6 (n= 78)	T12 (n= 71)	T0 (n= 74)	T6 (n= 74)	T12 (n= 67)
D-QoL sumscore	3.5 (0.32)	3.5 (0.32)	3.5 (0.33)	3.4 (0.24)	3.5 (0.31)	3.5 (0.27)
D-QoL aesthetics	3.5 (0.64)	3.5 (0.68)	3.6 (0.61)	3.4 (0.68)	3.5 (0.67)	3.6 (0.64)
D-QoL belonging	3.8 (0.50)	3.6 (0.50)	3.6 (0.48)	3.7 (0.44)	3.8 (0.45)	3.8 (0.40)
D-QoL negative affect	2.7 (0.54)	2.8 (0.47)	2.8 (0.53)	2.7 (0.47)	2.7 (0.53)	2.8 (0.49)
D-QoL positive affect	3.8 (0.41)	3.7 (0.47)	3.8 (0.44)	3.8 (0.39)	3.8 (0.43)	3.8 (0.39)
D-QoL self esteem	3.8 (0.48)*	3.8 (0.48)	3.9 (0.48)	3.6 (0.43)	3.7 (0.43)	3.7 (0.38)
SF12-MCS	55.5 (7.49)	55.9 (6.91)	55.8 (4.90)	53.8 (7.36)	54.6 (6.86)	54.8 (5.76)
SF12-PCS	47.9 (8.20)	47.4 (8.79)	49.8 (6.68)	49.1 (6.67)	49.6 (7.00)	50.6 (6.49)

MCI= Mild Cognitive Impairment; WP= Walking Program; PAP= Placebo Activity Program; FA/B12/B6= Folic Acid, vitamins B12 and B6; D-QoL= Dementia Quality of Life; SF12-MCS= Short Form 12 Mental Component Summary; SF12-PCS= Short Form 12 Physical Component Summary; [a] Higher rating indicates better QoL; * $p < 0.05$ (difference between FA/B12/B6 and placebo)

Modified intention-to-treat analysis

Results of the walking program and FA/B6/B12 supplementation are presented in Table 4. With respect to overall QoL, no positive significant main effect of the WP or FA/B6/B12 supplementation was found. A significantly detrimental effect of FA/B6/B12 supplementation was observed on D-QoL-belonging, (beta [95%CI]= -0.18 [-0.29; -0.07], $p < 0.01$). A positive interaction between the WP and attendance at the WP was observed on D-QoL-belonging and D-QoL-positive affect. With each percent increase in attendance, D-QoL-belonging increased by 0.003 points (p= 0.04) and D-QoL-positive affect by 0.002 points (p= 0.06) in the WP compared with the PAP. With respect to health-related QoL, an interaction between the WP and gender was observed on the SF12-MCS (p= 0.06) and therefore analysis for the SF12-MCS was stratified for gender. No main effects of the WP or FA/B12/B6-pills were observed. However, in men in the WP, SF12-MCS increased by 0.03 points with each percent increase in attendance (p= 0.08).

TABLE 4: The effects of the WP and FA/B6/B12 supplementation on change in QoL (adjusted model)

		WP (n= 77) vs. PAP (n= 75) Beta (95%CI)	p-value	FA/B12/B6 (n= 78) vs. placebo (n= 74) Beta (95%CI)	p-value
D-QoL sumscore		0.04 (-0.03; 0.10)	0.25	-0.06 (-0.12; 0.004)	0.07
D-QoL aesthetics		0.06 (-0.07; 0.20)	0.37	-0.07 (-0.20; 0.07)	0.33
D-QoL belonging		0.00 (-0.11; 0.11)	0.96	-0.18 (-0.29; -0.07)	0.00
D-QoL negative affect		-0.02 (-0.12; 0.08)	0.65	0.04 (-0.05; 0.14)	0.37
D-QoL positive affect		0.04 (-0.04; 0.13)	0.34	-0.04 (-0.12; 0.04)	0.33
D-QoL self esteem		0.08 (-0.02; 0.18)	0.11	0.00 (-0.10; 0.11)	0.94
SF12-PCS		0.66 (-1.23; 2.54)	0.49	-0.73 (-2.65; 1.19)	0.45
SF12-MCS*	men	-0.82 (-2.24; 0.60)	0.25	0.25 (-1.31; 1.81)	0.76
	women	1.66 (-1.50; 4.81)	0.30	1.32 (-1.93; 4.56)	0.42

WP= Walking Program; PAP= Placebo Activity Program; FA/B12/B6= Folic Acid, vitamins B12 and B6; D-QoL= Dementia Quality of Life; SF12-MCS= Short Form 12 Mental Component Summary; SF12-PCS= Short Form 12 Physical Component Summary; * Interaction WP and gender ($p < 0.10$)

Per protocol analysis

A subgroup analysis was performed in participants attending 75 percent or more of the WP and PAP sessions (n= 51, 33 men and 18 women). No between group differences were observed for FA/B12/B6-pills versus placebo-pills. A significant positive effect of the WP compared with the PAP was observed on D-QoL-positive affect, beta (95%CI)= 0.23 (0.06; 0.39), $p < 0.01$ and a borderline significant positive effect on D-QoL-self esteem, beta (95%CI)= 0.17 (0.001; 0.34), p= 0.05.

DISCUSSION

No positive main effect of walking or daily FA/B6/B12 supplementation was observed on QoL in community-dwelling adults with MCI. However, ratings of overall QoL (i.e. feelings of belonging, positive affect) and the mental component of health-related QoL improved slightly with increasing attendance at the walking program. In a subgroup that attended at least 75 percent of the sessions, a beneficial effect of the walking program was observed on positive affect and self esteem.

To our knowledge, this is the first intervention study on QoL in community-dwelling adults with MCI. While memory complaints are reported to be negatively associated with QoL in healthy older adults with subjective memory complaints[2], QoL ratings in our study population were already quite high at baseline. Baseline ratings on the DQOL sumscore and

subscales fell ample above the midpoint of the scale, except for negative affect. Baseline scores on the SF-12MCS fell around a half standard deviation above the average in the general population, and SF-12PCS fell about the average ratings. QoL-ratings have been reported to decrease as the severity of cognitive decline increases.[28] The possibility exists that MCI as operationalised in the present study may not have been serious enough to negatively influence overall and health-related QoL. In spite of the high baseline values, the QoL scales still allowed for further improvements, i.e. there was no ceiling effect. However, it has been discussed before that QoL may represent a stable concept which is difficult to change or that existing measures may not be responsive to subtle changes.[29]

The relationship between physical activity and QoL has been studied extensively. However, it is difficult to draw a clear conclusion, since various definitions and operationalisations of QoL circulate. Moreover, comparisons between studies are being complicated by the wide variety of study populations and features of exercise intentions such as intensity, exercise mode, frequency and session and total duration.[30] However, Rejeski et al.[31] concluded in a review including 28 studies, of which 11 RCT's, that physical activity positively influenced aspects of health-related QoL. In the recent meta-analysis by Netz et al.[7], including 36 studies, a small positive effect of exercise was observed on wellbeing in healthy older adults. In that meta-analysis four components of wellbeing were considered, including aspects that were also measured in the FACT-study, such as positive and negative affect, perception of physical fitness, and physical symptoms.

In the present study no main effects of the WP were observed in the modified intention-to-treat analysis. First, a possible explanation for the lack of effect may be that only participants with good QoL were able to attend enough sessions. In contrast to an earlier study, no baseline differences in number of chronic diseases, physical health-related QoL and aerobic fitness were observed between adherers (attending ≥ 75 percent of the sessions) and non-adherers (attending < 75 percent of the sessions).[32] However, adherers rated their mental health-related QoL at baseline significantly better than non-adherers. The difference was three points, which approximately equalled a difference of five percent. The possibility exists that participants with lower mental health-related QoL were inclined to attend less sessions. Nevertheless, it is not likely that this biased our results, because non-adherers and drop-outs from the exercise programs were included in the modified intention-to-treat analysis. In future studies in subjects with cognitive decline, session attendance may be improved by informing subjects extensively about the study aims and the consequences of participation. Moreover, if possible with respect to logistic and

financial issues, we advice to schedule time and staff for the close personal follow-up of temporary drop-outs.

Second, it has been reported that the association between physical activity and QoL is weaker among older adults who function at or above the norm.[31] By applying inclusion criteria for the present trial (e.g. community dwelling, no ADL disabilities, being able to perform moderate intensity physical activity), we presumably selected physically healthy and active participants. This is supported by the high baseline activity levels. Two-thirds of the participants reported to be physically active at moderate intensity for thirty minutes or more per day. Subjects meeting this guideline are reported to have better health-related QoL than physically inactive adults.[8] Additionally, Netz et al. found that larger effects of exercise on wellbeing were observed in sedentary adults.[7] However, in the present study, no interaction between the walking program and baseline physical activity level was observed (results not presented), indicating that inactive participants did not benefit more from the WP than active participants. Therefore, it is not likely that baseline physical activity level was a main cause of the lack of main effects.

Finally, inconclusive evidence is available about the intensity and exercise mode of physical activity required to benefit QoL. Netz et al.[7] concluded that aerobic training of moderate intensity was most beneficial for wellbeing. In a cross-sectional study, it was also observed that moderate intensity physical activity was positively related to health-related QoL.[8] In contrast, in a review by Spirduso and Cronin[33] no evidence of a relationship between exercise intensity and the rate of improvement in QoL was found. If the former was true, the possibility exists that the contrast between both programs in the present study would not have been large enough to induce differences in QoL. If the latter was true, participants would have benefited from participation in both exercise programs regardless of intensity. Both programs may have either improved self-efficacy, or may have prevented a decline in self-efficacy. The walking program by training aerobic fitness; the placebo activity program by training e.g. balance and ADL. Self-efficacy refers to somebody's belief that one has the capabilities to successfully manage situational demands and is thought to be a mediating mechanism for the effect of physical activity on QoL.[7,30,34,35] Thus, the presence of the low intensity placebo activity program in our study may have contributed towards the lack of between group differences.

Nevertheless, several outcomes improved with increasing attendance at the walking program. In the per protocol analysis, a beneficial effect was observed on positive affect. Self esteem also tended to improve. However, observed differences were small and

approximated five percent differences from baseline QoL ratings. As a rule of thumb, a minimal change of five percent has been suggested as an indicator of clinical relevance. To obtain a change of five percent by increasing attendance, the required increase in attendance would be 62 percent for D-QoL-belonging and 94 percent for D-QoL-positive affect and the SF12-MCS. Therefore, it can be questioned whether the observed effects are clinically relevant.

No effect of the FA/B12/B6 supplementation was observed except for a negative effect on feelings of belonging. However, no theoretical rationale exists for this effect. Our findings are in line with previous RCT's on the effect of vitamin B supplementation on aspects of QoL. Deijen et al.[12] observed no effect of supplementation with 20 milligrams vitamin B6 for three months on mood in healthy men (n= 76). Also no effect of supplementation with 750 micrograms folate, 15 micrograms vitamin B12 or 75 milligrams vitamin B6 daily for 35 days was observed on mood in women aged 65 or over (n= 75).[11] Finally, no effect on health-related QoL was observed of a weekly injection with 1 milligram vitamin B12 for four weeks in adults with vitamin B12 deficiency (n= 140).[13] These findings may originate from the used operationalisations, and measures of QoL that include very few items directly relating to nutrition. Amarantos et al.[36] underline the need to develop QoL measures including items that relate nutrition to QoL.

To conclude, the walking program and vitamin B supplementation were not effective in improving QoL in community-dwelling older adults with MCI within one year. However, increasing attendance at moderate intensity physical activity may benefit certain aspects of QoL.

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5.3

Feasibility of a moderate intensity walking program and effects on aerobic fitness and habitual physical activity in community-dwelling older adults with mild cognitive impairment

JGZ van Uffelen, MJM Chin A Paw, M Hopman-Rock, W van Mechelen
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ABSTRACT

Background

Mild cognitive impairment (MCI) is associated with poor physical health. Participation in moderate intensity physical activity induces important health benefits. However, no studies have been published yet on the feasibility and effects of exercise programs in elderly people with MCI.

Methods

One hundred and fifty-two community-dwelling adults 70 to 80 years of age with MCI were randomised to an intervention group; moderate intensity walking program (MI-WP, n= 77), or to a control group; low-intensity activity program (LI-AP, n= 75). Both programs included two sessions of one hour per week, for one year. Outcomes were measured at baseline, and after six and 12 months. Feasibility of the MI-WP was determined in terms of session attendance and compliance with program intensity, measured using heart rate monitors and Borg scales. To assess the effects of the MI-WP, aerobic fitness and physical activity levels were measured using a submaximal walking test and a physical activity questionnaire.

Results

Median attendance in participants attending at least one session was 70 percent. Percentage of heart rate reserve and Borg-scale scores were significantly higher in the MI-WP at all three measurements and commensurated with moderate intensity. Aerobic fitness, measured using a submaximal walking test, improved significantly in participants in the MI-WP (beta [95%CI]= 71.4 [8.3; 136.1] metres, p= 0.03).

Conclusion

The moderate intensity walking program was feasible in adults with MCI. Furthermore, aerobic fitness improved in participants participating regularly. These findings may have important public health implications.

INTRODUCTION

Regular participation in physical activity is an important modifiable risk factor for a number of age-related diseases such as cardiovascular disease, diabetes, osteoporosis[1,2] and enhances mental health.[3] Moreover, the benefits of exercise include reductions in morbidity and mortality, and enhanced functional capacity which leads to improvements in overall functioning.[4] To maintain physical fitness and to elicit health benefits, physical activity should at least be of moderate intensity.[1,5,6] Unfortunately, time spent in moderate intensity physical activities decreases with increasing age[7] and decreasing cognitive abilities.

It is of importance to enhance regular participation in physical activities, especially in those with cognitive decline, as indicated by Mild Cognitive Impairment (MCI). MCI is a potential transitional stage between normal cognitive function and Alzheimer's disease, characterised by: 1) memory complaints; 2) memory impairment; 3) normal mental status; 4) intact activities of daily living (ADL); and 5) absence of dementia.[8] MCI is associated with poor physical health and higher risk of ADL dependence.[9,10] The prevalence in the general population is three to four percent[11] and is likely to increase as the current generation of 'baby boomers' ages. To our knowledge, no trials have been published yet on the feasibility of exercise interventions nor on the effect on aerobic fitness and physical activity levels, of community-dwelling adults with MCI. Since higher levels of physical activity are associated with greater ADL independence and better cognitive function[1], this may be considered as a missed opportunity.

In the present study, the feasibility of a one year, twice weekly, group-based moderate intensity walking program in community-dwelling adults with MCI is evaluated. Furthermore, the effect of the walking program on aerobic fitness and habitual physical activity is examined, compared with a low intensity activity program.

METHODS

Study design and randomisation

This randomised controlled trial with a factorial design was originally designed to examine the effect of walking and vitamin supplementation on cognition. The study-protocol[12], including a sample size calculation for cognition, was approved by the medical ethics committee. In the present study, the moderate intensity walking program was compared with a low intensity activity program. Randomisation was stratified for baseline physical

activity level as measured by the LASA physical activity questionnaire[13] and was executed by the statistical program SPSS. Written informed consent was obtained from all participants.

Participants

Participants were recruited from the general population from September 2003 till January 2004. The operational criteria for MCI and additional inclusion criteria are described in Table 1. These criteria were checked using a postal questionnaire and a subsequent telephone interview.[14]

TABLE 1: Inclusion and exclusion criteria for participation in the trial

Operationalisation of Petersen criteria for MCI (1-5) and additional inclusion criteria for the RCT (6-12)
1. Memory complaints (answer yes to question 'do you have memory complaints', or at least twice sometimes at cognition scale of Strawbridge)
2. Objective memory impairment; 10 WLT delayed recall ≤ 5 + percentage savings ≤ 100
3. Normal general cognitive functioning; TICS ≥ 19 + MMSE ≥ 24
4. Intact daily functioning: no report of disability in activities of daily living on GARS-scale, except on the item 'taking care of feet and toe nails'
5. Absence of dementia; TICS ≥ 19 + MMSE ≥ 24
6. Being able to perform moderate intensity physical activity, without making use of walking devices, e.g. a rollator or a walking frame
7. Not using vitamin supplements/ vitamin injections/ drinks with high doses of folic acid, vitamins B12 and B6 comparable to doses as provided in vitamin supplementation intervention of the RCT
8. Not suffering from epilepsy, multiple sclerosis, Parkinson's disease, kidney disorder requiring haemodialysis, psychiatric impairment
9. Not suffering from depression as measured by the GDS (cut-off ≤ 5)
10. Not using medication for rheumatoid arthritis or psoriasis interfering with vitamin supplement as provided in vitamin supplementation intervention of the RCT
11. No alcohol abuse (men < 21 consumptions a week, women < 15 consumptions a week)
12. Not currently living in a nursing home or on a waiting list for a nursing home

MCI= Mild Cognitive Impairment; RCT= Randomised Controlled Trial; 10 WLT= 10 Word Learning Test; TICS= Telephone Interview for Cognitive Status; MMSE= Mini Mental State Examination; GARS= Groningen Activity Restriction Scale; GDS= Geriatric Depression Scale; See[12] for references of tests

Intervention

Both exercise programs were group-based with a frequency of two sessions of 60 minutes per week, for one year (June 2004- June 2005). Groups were supervised by qualified and trained instructors.

Moderate Intensity Walking Program (MI-WP)

The MI-WP was based on 'Sportive Walking', an existing aerobic walking program[15] and was designed to improve aerobic fitness. Moderate intensity was operationalised as walking at an intensity > 3 Metabolic Equivalents (MET). Exercise intensity was monitored subjectively during the classes by the instructors. The criteria were that participants were still able to talk, but also showed signs of moderate intensity physical activity, e.g. increased breathing frequency, turning red, transpiration. Each session consisted of a warm-up, moderate intensity walking, and a cool-down. Participants were able to exercise at their own level, without loosing the connection with the group. They were taught to walk at four walking paces (0, 1, 2, 3). Pace zero corresponded to quiet walking and pace three to brisk walking. The intensity of the MI-WP increased gradually during the program by increasing the time spent in walking at pace three. Sessions took place outdoors in municipal parks and were only cancelled when it was slippery due to snow or freezing rain.

Low Intensity Activity Program (LI-AP)

Intensity of the LI-AP was operationalised as activity at an intensity < 3 MET. Participants were taught to recognise signs of becoming too intensely active and instructed to decrease intensity if they experienced them. This was subjectively monitored by the instructors. The program consisted of an introduction, low intensity non-aerobic group exercises, and a closing. Sessions were divided into five themes: relaxation, activities of daily living, balance, flexibility and posture. For each theme and the combination of all, three sessions were developed. The entire series of 18 sessions was repeated. The program was carried out in community centres.

Measurements

The measurement of baseline variables has been described elsewhere.[12] For all outcomes except attendance, data were collected at baseline and after six and 12 months of intervention. Data on effects were collected by examiners blinded to group allocation. Blinded collection of feasibility data was not possible.

Feasibility

Attendance

Attendance was defined as the percentage of attended sessions during the intervention.

Compliance with program intensity

Resting heart rate (HR-rest) was recorded after ten minutes rest preceding the session, using heart rate monitors (Polar, Vantage NV). Subsequently, heart rate was recorded every minute during the session. Next, the mean heart rate (HR-mean) during moderate intensity walking in the MI-WP and during the non-aerobic group exercises in the LI-AP was calculated. Maximum heart rate (HR-max) was estimated by the following equation: HR-max= 208 – (0.7*age).[16] Finally, percentage of heart rate reserve (%HRR) was calculated using the following formula: %HRR= (HR-mean – HR-rest)/ (HR-max – HR-rest).[17] Exclusion criteria for heart rate measurement were use of beta blockers, having a pacemaker, or having current heart problems. During the sessions in which heart rate was recorded, subjective program intensity was assessed immediately after the core of the program by administering the Borg-scale. This is a measure of perceived exertion, based on a 15 item scale from 6 (no exertion at all) to 20 (maximum exertion).[18]

Effects

Aerobic fitness: Groningen Walking Test (GWT)

The GWT is a graded sub-maximal test for aerobic fitness (walking endurance) for the elderly.[19] Participants in the GWT walked distances of 16.6 metres between pylons in a large rectangle. For every covered distance, one point was scored. Walking speed started at four km/hr, increasing every three minutes by one km/hr to a maximum of seven km/hr. The test was finished if the participant failed twice to reach the next pylon in time. The maximum score was 66 points, which corresponded to a walking distance of 1.1 kilometres. Before participation in the GWT or the interventions, participants completed the physical activity readiness questionnaire[20] and in cases where some doubt about the ability to participate existed, consulted their general practitioner.

Habitual physical activity: LASA Physical Activity Questionnaire (LAPAQ)

The LAPAQ[13] was interviewer-administered. Participants were asked how often and for how long they had engaged in the previous two weeks in: walking, bicycling, gardening, light effort household tasks, vigorous effort household tasks and a maximum of two sports. For each activity, participation in minutes per day was calculated and metabolic equivalents (METs) were ascribed [21] (Table 2). Finally, MET-intensity of the activities was classified according to the classification proposed by Pate et al (1995): low intensity < 3 METs; moderate intensity 3-6 METs; high intensity > 6 METs.[6]

TABLE 2: LAPAQ-items and corresponding MET-values

LAPAQ	Metabolic Equivalents (MET)[a,b]		
Habitual physical activities	Major type of activity	Specific activity	MET-value
walking (4 km/h)	walking	walking, 2.5 mph, firm surface	3
bicycling (16-19 km/h)	bicycling	bicycling 10-11.9 mph, leisure, light effort	6
gardening	lawn + garden	gardening general	4
household tasks, light effort	home activities	multiple household tasks, all at once light effort	2.5
household tasks, vigorous effort	home activities	multiple household tasks, all at once, vigorous effort	4
Sports activities			
walking for pleasure (5.6 km/h)	walking	walking, 3.5 mph, firm surface, walking for exercise	3.8
bicycling (19-22 km/h)	bicycling	bicycling 12-13.9 mph, leisure, moderate effort	8
gymnastics	sports	gymnastics general	4
bicycling stationary, hometrainer	conditioning exercise	bicycling stationary, general	7
swimming	water activities	swimming laps, freestyle slow, moderate or light effort	7
dancing	dancing	dancing, general	4.5
bowling/ play ninepins/ play boules	sports	bowling	3.0
badminton/tennis[c]	sports	badminton general (MET 4.5); tennis, general (MET 7)	5.8
jogging/ running/ heel-and-toe walking	running	jogging, general	7
rowing	conditioning exercise	rowing, stationary ergometer, general	7
sailing	water activities	sailing, boat sailing, general	3
billiards	sports	billiards	2.5
fishing	fishing + hunting	fishing, general	3.0
soccer/ basketball/ korfball[c]	sports	soccer, casual, general (MET 7); basketball, non game, general (MET 6)	6.5
volleyball/ baseball	sports	softball or baseball, fast or slow pitch, general (met 5) volleyball (MET 4)	4.5
winter sports[c]	winter activities	skating, ice, general/ skiing, general/ skiing, cross country (all MET 7)	7

LAPAQ= LASA Physical Activity Questionnaire; [a] Data derived from the compendium of physical activities[21]; [b] 1 MET= 3.5 ml oxygen/ kg/min, or 1 kcal/kg/hour[17]; [c] Mean METs of specific activities

Statistical analysis

Differences between participants in the MI-WP and participants in the LI-AP were tested using independent t-tests, Mann Whitney U tests or chi-square tests. Intention-to-treat analysis was performed including data from participants with at least one post-baseline assessment, using longitudinal regression analysis. The two follow-up measurements were defined as dependent variable and multi-level analysis with two levels was used, 1) time of follow-up measurement (values corresponding with performance after six and 12 months intervention); 2) individual. Data were analysed using a crude and an adjusted model. Reported regression coefficients indicate the differences between the MI-WP and the LI-AP. In the crude model, the independent variable was exercise intervention. Baseline values of

the outcome variables were added as covariate. Moreover, since half of the participants received vitamin pills, vitamin intervention was added as a covariate. In the adjusted model, gender, education, body mass index (BMI) and attendance at the exercise programs were added as covariates. Three interaction terms were checked: 1) MI-WP and gender; 2) MI-WP and attendance; and 3) MI-WP and BMI. Data were analysed using SPSS (release 12.0.1). The significance level was set to five percent for between-group comparisons and ten percent for interaction terms.

RESULTS

Participant flow and characteristics

One hundred and fifty-two participants provided LAPAQ-data at baseline and at at least one follow-up measurement. See Figure 1 for participant flow. Baseline variables are described in Table 3. The MI-WP included significantly fewer men than the LI-AP (48% versus 64%) and significantly more participants with hypertension (27% versus 14%). Borg and heart rate data were available from participants who attended the exercise sessions in which such measurements were performed. At baseline, participants who provided Borg data (n= 74) differed from participants without Borg data (n= 78) with respect to AVLT delayed recall (mean [SD]= 6.3 [2.6] versus 5.4 [2.2], p= 0.04), and minutes spent per day in moderate intensity physical activity (median [10^{th}; 90^{th} percentile]= 45 [10; 118] versus 56 [18; 164], p= 0.03). Participants with heart rate recordings (n= 54) reported significantly fewer chronic diseases than participants without heart rate recordings (n= 98), p= 0.03. No significant baseline differences were observed between participants with (n= 89) and without GWT data (n= 63). Baseline values of the measurements, and values after six and 12 months intervention are reported in Tables 4a and 4b.

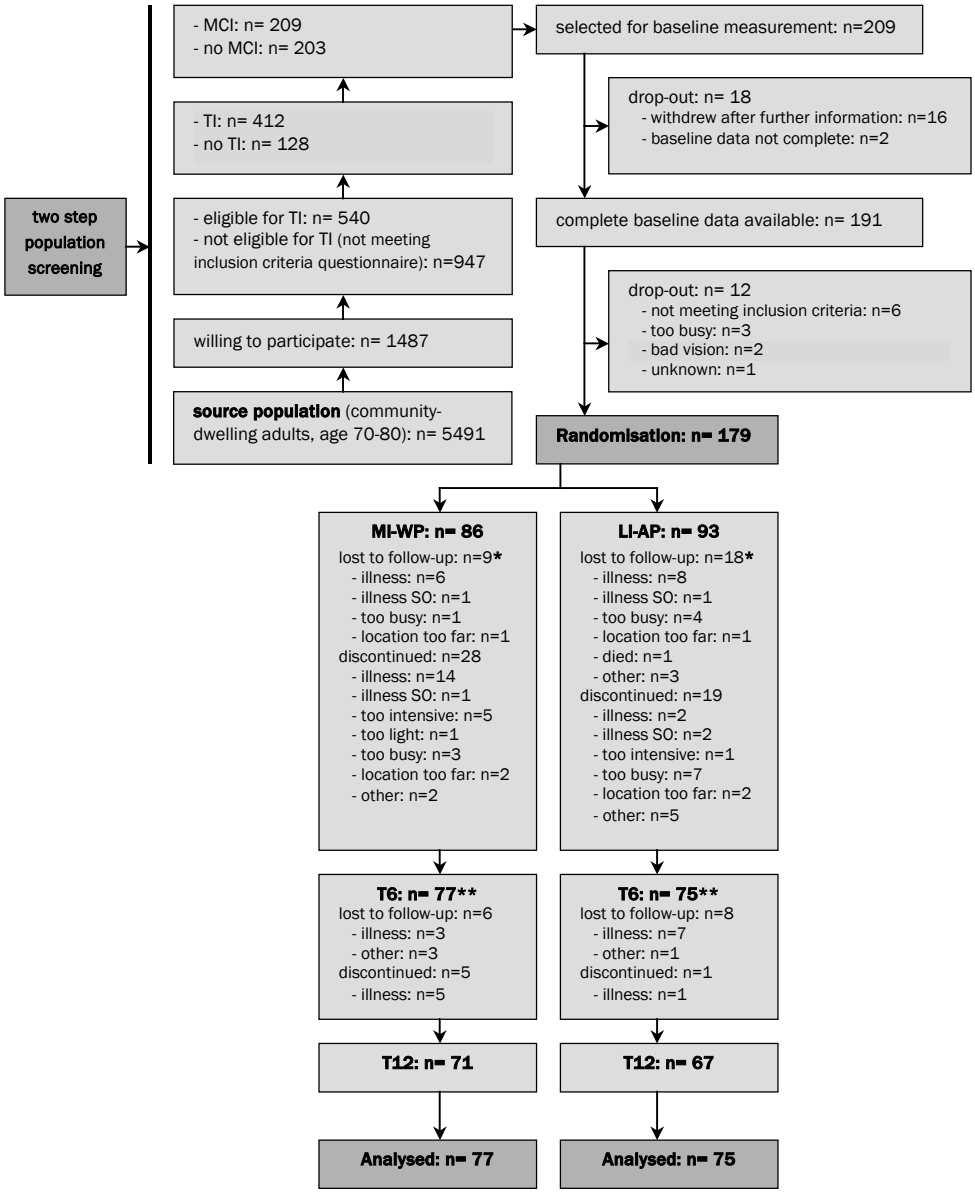

FIGURE 1: Flow chart

TI= Telephone Interview; MCI= Mild Cognitive Impairment; MI-WP= Moderate Intensity Walking Program; LI-AP= Low Intensity Activity Program; SO= Significant Other; T6= Follow-up after 6 months; T12= Follow-up after 12 months; * Excluded from analysis (only baseline data); ** Included in analysis

TABLE 3: Baseline characteristics of participants (n= 152)

	MI-WP (n= 77)	LI-AP (n=75)
Age, years (Mean (SD))	75 (2.9)	75 (2.8)
Gender (% male)	48*	64
MMSE (Median (10^{th}; 90^{th} ‰))	29 (26; 30)	29 (27; 30)
AVLT direct recall (Mean (SD))	33.7 (8.0)	31.8 (7.6)
AVLT delayed recall (Mean (SD))	6.1 (2.5)	5.6 (2.3)
Education (% low/intermediate/high)[a]	61/22/17	52/29/19
Marital status (% living with partner)	75	68
Blood pressure (% hypertension)[b]	27*	14
BMI (kg/m2) (Mean (SD))	26.8 (3.2)	27.4 (3.5)
Smoking (% smokers)	13	15
Number of self-reported diseases (% 0,1,2)[c]	52/42/6	69/27/4

MI-WP= Moderate Intensity Walking Program; LI-AP= Low Intensity Activity Program; MMSE= Mini Mental State Examination; AVLT= Auditory Verbal Learning Test; BMI= Body Mass Index; [a] *low*= no education, primary education, lower vocational training, *intermediate*= intermediate level secondary education, intermediate vocational training, *high*= higher level secondary education, higher vocational training, university training; [b] Hypertension= diastole ≥ 90 and systole ≥ 160; [c] Cardiovascular disease, chronic obstructive pulmonary disease, diabetes, epilepsy, multiple sclerosis, Parkinson's disease, psychiatric disease, renal failure requiring dialysis and/or rheumatoid arthritis; * Significantly different from LI-AP ($p<0.05$)

TABLES 4a and 4b: Measures of intensity and values of the outcome measures at baseline and after six and 12 months - MI-WP versus LI-AP

4a		Moderate Intensity Walking Program (MI-WP)					
		T0	n	T6	n	T12	n
Compliance: comparison between the MI-WP and LI-AP at T0, T6 and T12							
% HRR (Median (10^{th}; 90^{th} ‰))		27 (13; 54)*	21	37 (19; 69)*	21	40 (25; 67)*	12
Borg scales (Mean (SD))		11.6 (1.5)*	31	13.1 (1.4)*	31	12.6 (1.4)*	18
Outcome measures: comparison between the MI-WP and LI-AP at T0							
GWT (Median (10^{th}; 90^{th} ‰))		37 (27; 52)	43	43 (28; 53)	40	47 (28; 66)	40
LAPAQ (min/day) (Median (10^{th}; 90^{th} ‰))	low (3 METs)	60 (20; 180)	77	60 (15; 150)	77	60 (15; 144)	71
	moderate (3-6 METs)	54 (13; 135)	77	60 (17; 174)	77	51 (18; 133)	71
	high (6 METs)	9 (0; 47)	77	15 (0; 66)	77	14 (0; 59)	71

4b		Low Intensity Activity Program (LI-AP)					
		T0	n	T6	n	T12	n
Compliance: comparison between the MI-WP and LI-AP at T0, T6 and T12							
% HRR (Median (10^{th}; 90^{th} ‰))		14 (8; 27)	33	16 (9; 27)	29	19 (10; 34)	24
Borg scales (Mean (SD))		10.8 (1.5)	43	11.1 (1.6)	40	11.7 (1.7)	33
Outcome measures: comparison between the MI-WP and LI-AP at T0							
GWT (Median (10^{th}; 90^{th} ‰))		30 (15; 56)	46	29 (16; 61)	44	36 (16; 66)	39
LAPAQ (min/day) (Median (10^{th}; 90^{th} ‰))	low (3 METs)	60 (15; 150)	75	45 (15; 120)	75	34 (7; 120)	67
	moderate (3-6 METs)	46 (13; 141)	75	57 (11; 146)	75	47 (19; 125)	67
	high (6 METs)	10 (0; 42)	75	15 (0; 63)	75	10 (0; 60)	67

% HRR= Percentage of Heart Rate Reserve; GWT= Groningen Walking Test; LAPAQ= Longitudinal Aging Study Amsterdam Physical Activity Questionnaire; METs= Metabolic Equivalents; * Different from LI-AP ($p<0.05$)

Feasibility

Attendance

Program attendance is reported in Table 5. Thirty participants did not attend a single session. In the remaining 122 participants, median attendance (10^{th}; 90^{th} percentile) was 70 (6; 86) percent to the MI-WP and 71 (9; 92) percent to the LI-AP. Attendance at the LI-AP was significantly higher, p= 0.03. No adverse events of the MI-WP or LI-AP were reported. Spearman's correlation coefficients between attendance and both the MMSE-score and AVLT delayed recall were non-significant (r= 0.14 and r= 0.12 respectively).

TABLE 5: Distribution of the participants over five categories of attendance

	Percentage of attended sessions					
	0%	1-24 %	25-49 %	50-74 %	75-100 %	Total
MI-WP (n)	15	15	8	16	23	77
LI-AP (n)	15	6	9	17	28	75
Total (n)	30	21	17	33	51	152

MI-WP= Moderate Intensity Walking Program; LI-AP= Low Intensity Activity Program

Compliance with program intensity

Both percentage of heart rate reserve and self rated intensity were significantly higher in the MI-WP at baseline and after six and 12 months intervention (Tables 4a and 4b).

Effects

Aerobic fitness: GWT

A beneficial main effect of the MI-WP was found on the GWT-score (n= 89), beta (95%CI)= 71.4 (8.3; 136.1) metres, $p < 0.05$ (Table 6).

Habitual physical activity: LAPAQ

A significant intervention effect on low intensity activity was observed (beta [95%CI]= 13.6 [2.9; 24.3] min/day, $p < 0.05$) (Table 6). For high intensity physical activity, a significant interaction between the MI-WP and attendance was observed. With each percent increase in attendance, time spent in high intensity physical activity increased by 0.16 minutes per day (beta [95%CI]= 0.16 [-0.01; 0.34] min/day, p= 0.07).

Table 6: The effect of the Moderate Intensity Walking Program on change in distance covered during the GWT (n= 89) and LAPAQ values (n= 152)

	MI-WP versus LI-AP Beta (95%CI), crude model[a]	p-value	MI-WP versus LI-AP Beta (95%CI), adjusted model[b]	p-value
GWT (metres)	63.1 (0.7; 124.5)	0.047	71.4 (8.3; 136.1)	0.03
LAPAQ low intensity[c] (min/day)	16.0 (5.1; 26.9)	0.004	13.6 (2.9; 24.3)	0.01
LAPAQ moderate intensity[d] (min/day)	4.3 (-11.1; 19.7)	0.58	8.3 (-7.2; 23.7)	0.29
LAPAQ high intensity[e] (min/day)	2.1 (-4.0; 8.3)	0.50	3.2 (-3.2; 9.6)	0.33

MI-WP= Moderate Intensity Walking Program; LI-AP= Low Intensity Activity Program; GWT= Groningen Walking Test; LAPAQ= Longitudinal Aging Study Amsterdam Physical Activity Questionnaire; [a] Crude model: adjusted for time, vitamin supplementation and baseline value outcome; [b] Adjusted model= crude model + additionally adjusted for gender, education, BMI, session attendance; [c] < 3 MET; [d] 3-6 MET; [e] > 6 MET; MET= Metabolic Equivalents

DISCUSSION

The results of this RCT show that participation in a group-based moderate intensity walking program is feasible for community-dwelling adults with MCI: median attendance in participants who started the program was 70 percent, and compliance with program intensity was good, i.e. both objective and subjective measures of program intensity indicated that the intensity was moderate. Attendance was not related to general cognitive function or memory. The MI-WP was effective in improving aerobic fitness compared with a low intensity activity program.

Actual drop-out rate was higher than the a priori assumed rate of 25 percent.[12] Fifty-seven out of 179 randomised participants (32 percent) did not attend a single session. Thirty of these participants were included in the intention-to-treat analysis, because they completed the physical activity questionnaire at six and/or at 12 months follow-up. This may have underestimated the actual intervention effect. A frequently mentioned reason for drop-out was lack of interest. Premature drop-out may be reduced by informing subjects properly about study aims and the nature of the intervention. Especially in a population with MCI, a single brochure may not suffice.

Attendance in participants who attended at least one session (n= 122) corresponded to the mean attendance of 63 to 84 percent as reported in a review on group-based physical activity interventions in older adults.[22] The small, but significantly, higher attendance at the LI-AP was in line with a review reporting that adherence tends to be higher in flexibility

programs than in aerobic exercise programs.[23] In line with the literature, health-related problems were the main reason for discontinuation after the start of the program.[24,25]

Concerning compliance with program intensity, percentage of heart rate reserve and Borg data corresponded to moderate effort in the MI-WP and light effort in the LI-AP at six and 12 months follow-up according to common cut-off points for intensity.[17] For the purpose of this study, larger differences in program intensity would have been preferred to increase contrast between both exercise programs. However, the MI-WP was effective in improving aerobic fitness, even despite the fact that a large proportion of participants reported at baseline to already meet current physical activity guidelines. A probable explanation for the high self-reported physical activity levels is that subjects are liable to overestimate frequency and duration of physical activities.[26] It should be emphasised that data on program intensity and GWT data are based on an adherent sub-group of the total study-population. Therefore, these results only apply for participants who regularly participated in the MI-WP.

Against expectations, the MI-WP did not increase self-reported time spent in moderate and high intensity physical activity as measured using the LAPAQ. In general, questionnaires are suitable for assessing physical activity levels of groups in epidemiologic research.[26,27] The LAPAQ has been shown to be a valid and reliable instrument for classifying physical activity in older Dutch adults.[13] However, Shepard (2002) concludes that physical activity data obtained by questionnaires have limited reliability and validity.[26] A drawback of physical activity questionnaires is that they rely on subjects' recall of physical activity behavior.[27] Therefore, the applicability of physical activity questionnaires in this population with MCI can be questioned. Moreover, the LAPAQ may not have been sensitive enough to detect differences in physical activity levels induced by our interventions. Objective activity monitors such as pedometers or accelerometers provide more accurate insight in actual physical activity level.[27,28] However, drawbacks would be difficulties in recording activities such as cycling or walking at a 'shambling' pace. Also, logistic problems may arise in large studies.

To conclude: MCI did not interfere with the ability to participate in moderate intensity exercise and a positive effect was observed on aerobic fitness in participants who attended the walking sessions regularly. Since the number of adults with cognitive decline is likely to increase in the future, these results are of particular importance with respect to public health, given the multiple benefits of improved fitness. The present study provides further evidence for the enhancement of participation in moderate intensity physical activity or exercise in older adults with MCI.

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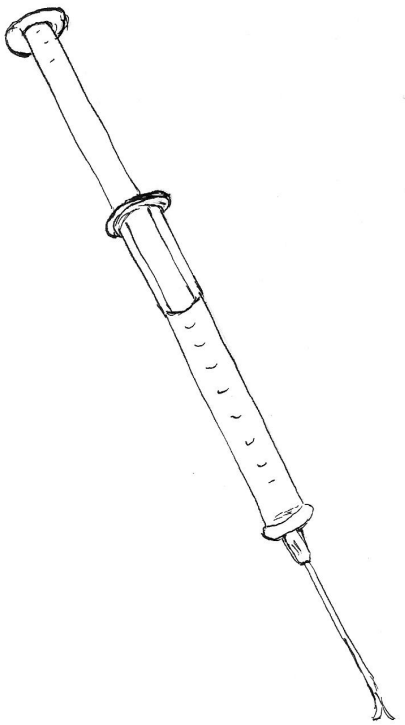
5.4

The effects of folic acid, vitamins B12 and B6 and physical exercise on homocysteine concentrations in community-dwelling older adults with mild cognitive impairment



JGZ van Uffelen, M Gavrovska, W van Mechelen, M Hopman-Rock, MJM Chin A Paw, Submitted for publication

ABSTRACT

Background

Since the number of people with cognitive decline and dementia is growing, it is important to examine interventions that may decrease the rate of cognitive decline. Increased homocysteine concentrations are an independent risk factor for dementia. This study investigated the effects of folic acid, vitamin B12 and vitamin B6 supplementation and moderate intensity aerobic exercise on homocysteine concentrations in older community dwelling adults with mild cognitive impairment.

Methods

The study was designed as a randomised, placebo-controlled intervention trial with a two-by-two factorial design. One hundred and fifty-two participants, aged 70 to 80 years, were randomly assigned to one year of 1) daily vitamin pills containing 5 mg folic acid, 0.4 mg vitamin B12 and 50 mg vitamin B6 (n= 78) or placebo pills (n= 74); and 2) a twice-weekly, group-based, moderate-intensity walking program designed to improve aerobic fitness (n= 77) or a low-intensity placebo activity program (n= 75). At baseline and after six and 12 months intervention, blood samples were collected to determine concentrations of homocysteine, folate, vitamin B12 and vitamin B6.

Results

Median compliance was 100 percent with the vitamin supplementation and 51 percent with the walking program. Plasma homocysteine concentrations significantly decreased in the vitamin supplementation group (between group difference [95% CI]= -3.7 [-4.5; -3.0] micromol/liter and –4.9 [-5.7; -4.0] micromol/liter after six and 12 months follow-up). Also, the prevalence of hyperhomocysteinemia decreased significantly in the vitamin supplementation group, while a significant increase was observed in the placebo group. No significant differences in homocysteine concentrations were observed between participants in the walking program and participants in the placebo activity program.

Conclusion

Twelve months of supplementation with folic acid, vitamin B12 and vitamin B6 significantly reduced plasma homocysteine concentrations and prevalence of hyperhomocysteinemia in people with MCI, while moderate intensity aerobic exercise did not.

INTRODUCTION

Since both the number of older adults and their life expectancy is increasing, the incidence and prevalence of cognitive impairment and dementia is growing. Mild cognitive impairment (MCI) is considered to be a stage in-between normal cognitive function and dementia[1] and seems a promising stage at which to intervene with preventive therapies intended to decrease the rate of cognitive decline.[2,3]

Increased homocysteine concentrations (>14 micromol/liter) appear to be a strong and independent risk factor for dementia and Alzheimer's disease.[4] Increased plasma homocysteine concentrations have been shown to be associated with decreased cognitive performance in cognitively healthy subjects[5-7] and in subjects with MCI.[8] Quadri et al. (2004) observed that the proportion of subjects with increased homocysteine concentrations (>14.6 micromol/liter) increased from 31 percent in older cognitively healthy adults, to 42 percent in subjects with MCI, to 55 percent in subjects with Alzheimer's disease.[9]

Lehmann et al. (2003) hypothesised that increased homocysteine concentrations as a vasotoxic agent leading to damaging of the blood-brain barrier, which might play an important role in the development of cognitive decline and dementia.[10] Since increased homocysteine concentrations appear to be an early predictor for cognitive decline in elderly people, the identification of interventions that influence homocysteine concentrations in advanced age warrants further examination.[11]

Deficiencies of folate and vitamins B12 and B6 lead to increased homocysteine concentrations, since they are co-factors in homocysteine metabolism.[12] Unfortunately, vitamin B deficiency is common among older adults, even in the presence of normal serum vitamin concentrations.[11,13] The combination of folic acid, vitamin B12 and vitamin B6 supplementation has been shown to be effective in lowering plasma homocysteine concentrations in healthy older adults[14], in people with MCI and hyperhomocysteinemia[10], and in those with Alzheimer's disease.[15] In the present study, the effect of supplementation with folic acid, vitamin B6 and vitamin B12 was studied in community-dwelling adults with MCI, who were not recruited on the basis of hyperhomocysteinemia or vitamin B deficiency.

Physical activity level may also be a modifiable factor influencing plasma homocysteine concentrations. The Hordaland Homocysteine Study, including a large population of adults in Norway, found that increased plasma homocysteine concentrations were associated with

a lack of physical activity.[16] De Bree et al. (2001) observed a weak positive relationship between homocysteine and physical activity levels in women only.[17] Few intervention studies have examined this relationship and the findings are contradictory. Only one randomised controlled trial has examined the effect of exercise on homocysteine concentrations in frail, community-dwelling older people and found no effect after 17 weeks twice-weekly moderate intensity exercise training.[18] To our knowledge, the effect of exercise training on homocysteine concentrations has not been examined yet in subjects with MCI. In light of the association between homocysteine concentrations and cognitive decline, it is of public health importance to gain more insight into the potential beneficial influence of exercise training on homocysteine concentrations in this population.

The primary objective of the FACT-study (Folate physical Activity Cognition Trial) was to examine the effect of two interventions on cognitive function.[19] In this paper, the effect of one year of daily vitamin supplementation (5 mg folic acid, 50 mg vitamin B6 and 0.4 mg vitamin B12) and of moderate intensity walking (two sessions of 60 minutes per week) on plasma homocysteine concentrations in community-dwelling older adults with MCI was examined.

METHODS

Study design and sample size

The study was designed as a randomised, placebo-controlled intervention trial with a two-by-two factorial design. The study-protocol has been described in detail elsewhere[19] and was approved by the VU University Medical Center medical ethics committee. Written informed consent was obtained from all participants.

The a priori sample size calculation was based on expected changes in cognitive outcome measures. For this study, a post hoc sample size calculation with a power of 0.8 and an alpha of 0.05 showed that the sample size of 152 participants, 76 per group, could demonstrate a between-group difference of 1.50 micromol/liter in plasma homocysteine concentrations.

Randomisation and blinding

After the baseline interview, participants were randomised using the option ‘random sample of cases’ in SPSS. Randomisation was stratified for physical activity level as measured by the LASA physical activity questionnaire.[20] Intervention groups were: 1) vitamin B supplementation or placebo supplementation; and 2) walking program or placebo activity

program. The study was conducted as a double-blind trial. The pills were coded as A or B by the manufacturer. The key was decoded after data-analysis. Participants and instructors were blinded for the exercise intervention by being left unaware of which exercise program was supposed to be effective. Blood samples were collected by laboratory assistants blinded to group allocation; cognitive outcome measures were assessed by blinded examiners.

Study population

All community-dwelling inhabitants 70 to 80 years of age in a Dutch town (n= 5491) were sent an invitation letter for participation in the RCT in September 2003. Of those willing to participate in the RCT, adults with MCI were identified using a two-step screening consisting of a postal screening questionnaire and a telephone interview for general cognitive status and memory, in which inclusion criteria were checked. The recruitment procedure has been described in detail elsewhere.[21] Operational criteria for MCI and additional inclusion criteria for the trial are described in Table 1.

TABLE 1: Inclusion and exclusion criteria for participation in the trial

Operationalisation of Petersen criteria for MCI (1-5) and additional inclusion criteria for the RCT (6-12)
1. Memory complaints (answer yes to question 'do you have memory complaints', or at least twice sometimes at cognition scale of Strawbridge[22])
2. Objective memory impairment; 10 WLT[23] delayed recall ≤ 5 + percentage savings ≤ 100
3. Normal general cognitive functioning; TICS[24] ≥ 19 + MMSE ≥ 24[25]
4. Intact daily functioning: no report of disability in activities of daily living on GARS-scale[26], except on the item 'taking care of feet and toe nails'
5. Absence of dementia; TICS ≥ 19 + MMSE ≥ 24
6. Being able to perform moderate intensity physical activity, without making use or walking devices, e.g. a rollator or a walking frame
7. Not using vitamin supplements/vitamin injections/drinks with dose of folic acid, vitamins B12 or B6 comparable to vitamin supplement given in intervention
8. Not suffering from epilepsy, multiple sclerosis, Parkinson's disease, kidney disorder requiring haemodialysis, psychiatric impairment
9. Not suffering from depression as measured by the GDS[27] (cut-off ≤ 5)
10. Not using medication for rheumatoid arthritis or psoriasis interfering with vitamin supplement
11. No alcohol abuse (men < 21 consumptions a week, women < 15 consumptions a week)
12. Not currently living in a nursing home or on a waiting list for a nursing home

MCI= Mild Cognitive Impairment; RCT= Randomised Controlled Trial; 10 WLT= 10 Word Learning Test; TICS= Telephone Interview for Cognitive Status; MMSE= Mini Mental State Examination; GARS= Groningen Activity Restriction Scale; GDS= Geriatric Depression Scale

Interventions

Both interventions (vitamin supplementation and exercise) lasted from June 2004 till June 2005. Participants randomised to the vitamin group received one pill daily containing 5 mg vitamin B11 (folic acid), 0.4 mg vitamin B12 (Cyanocobalamin) and 50 mg vitamin B6 (Pyridoxine-hydrochloride) for a year (FA/B12/B6). These vitamin supplements are available on prescription in The Netherlands. For the purpose of this study, the package and vitamin pills could not be identified as an existing supplement. Participants in the control group received an identically looking placebo pill. Pills were calendar packed in blister packs that were labelled for each day of the week.

Exercise sessions for both programs were held twice each week under the supervision of qualified staff and lasted one hour. Participants in the moderate intensity (> 3 Metabolic equivalents) walking program (WP) participated outdoors in walking training designed to improve aerobic fitness.[28] Intensity was gradually increased, based at individual capacity. Participants in the low intensity (< 3 metabolic equivalents) placebo activity program (PAP) performed non-aerobic exercises for relaxation, balance, flexibility, posture and activities of daily living.

Data collection

Blood

Non-fasting blood samples were taken to determine homocysteine and blood vitamin concentrations. Plasma concentrations of homocysteine, serum folate and vitamin B12 in serum were determined by a competitive immunoassay using direct chemiluminescent technology (ADVIA CENTAUR, Bayer Corporation, Tarrytown, USA). Vitamin B6 in plasma was measured using high performance liquid chromatography with fluorescence detection using Chromopack Lichrosorb RP-18 columns (Varian Inc., Palo Alto, USA) and the Jasco HPLC system (Jasco Benelux, Maarssen, The Netherlands). The following cut-off points for hyperhomocysteinemia and vitamin B deficiency were used: hyperhomocysteinemia (plasma homocysteine concentration > 14 micromol/liter[29]); folate deficiency in serum (folate in serum < 6.3 nanomol/liter[18]); vitamin B12 deficiency (vitamin B12 concentration in serum < 150 picomol/liter[30]); vitamin B6 deficiency (vitamin B6 concentration in plasma < 20 nanomol/liter [31]).

Cognition, physical activity and anthropometry

All participants were invited for a personal interview at baseline, and at follow-up after six and 12 months. General cognitive function was assessed using the Mini Mental State Examination (MMSE).[25] The MMSE consists of 11 questions concerning orientation,

registration, attention and calculation, recall and language. The maximum score is 30 and a score below 24 is considered abnormal for dementia screening.[25] Verbal learning memory was assessed using the Auditory Verbal Learning Test (AVLT).[32] This is a measure of verbal memory in which direct and delayed recall are assessed. During the test a list of 15 non-symbolic words is read aloud by the examiner for five times. After each trial the subject is asked to repeat the words he or she remembers. After fifteen minutes with other questions, delayed recall is assessed by asking the participant which words he or she remembers.

Physical activity level was assessed using the LASA Physical Activity Questionnaire (LAPAQ)[20], which was administered in a personal interview. The LAPAQ addresses the following activities: walking outdoors, bicycling, gardening, light household activities, heavy household activities, and a maximum of two sports activities. Respondents were asked how often and for how long they had engaged in each activity in the previous two weeks. Two measures of total daily physical activity were composed: 1) total physical activity level (minutes/day); and 2) moderate intensity physical activity level (minutes/day) (≥ 3.0 metabolic equivalents).

Blood pressure was recorded using a digital blood pressure device (Omron M5-1), after five minutes rest in a seated position. Body height (m) and weight (kg) were measured according to standardised procedures and BMI was calculated as body weight (kg) divided by height (m^2).

Statistical analysis

Between-group differences in baseline characteristics were tested using independent t-tests, Mann Whitney U tests and chi-square tests. Spearman correlations between homocysteine concentrations and blood vitamin concentrations and physical activity level were calculated to determine associations at baseline. The effect on homocysteine concentrations was compared between baseline and six months follow-up and baseline and 12 months follow-up. Data were analysed according to an intention-to-treat principle, including participants with at least one post-baseline assessment, using linear regression analysis. Since there was no evidence of interaction between the interventions, analysis was performed by factor. In the crude model, independent variables were vitamin intervention, exercise intervention, and baseline homocysteine concentration.

In the adjusted model, gender, age and session attendance were added as covariates. Effect modification by gender was checked by adding two interaction terms: 1) gender and vitamin intervention; and 2) gender and exercise intervention. Regression coefficients and 95% confidence intervals were reported, indicating between-group differences. Data were analysed using SPSS (release 12.0.2). A significance level of five percent was used for between-group comparisons and ten percent for interaction terms.

RESULTS

Participant flow and characteristics

One hundred and seventy-nine participants were randomised to: 1) vitamin supplementation (n= 90) or placebo supplementation (n= 89); or 2) WP (n= 86) or PAP (n= 93). Data from 152 participants who provided data at baseline and at least one follow-up were included in the analysis. See Figure 1 for flow chart. Their mean age (SD) was 75 (2.9) years and 56 percent were male. Additional baseline characteristics are reported by factor in Table 2. Compared with the PAP, the WP included significantly fewer men (48% in WP versus 64% in PAP) and more participants with hypertension (27% in WP versus 14% in PAP).

Compliance and attendance

Compliance with the vitamin and placebo pills was almost 100 percent as determined on the basis of pill counts in returned blister packs and blood vitamin and homocysteine concentrations. Four participants did not return the blister packs. Two participants stopped taking vitamin pills after reporting sleep problems and increased forgetfulness; one participant discontinued the placebo-pills after reporting not feeling well. Median session attendance during the total intervention period was 51 percent at the WP and 53 percent at the PAP. No adverse events of the WP or PAP were reported.

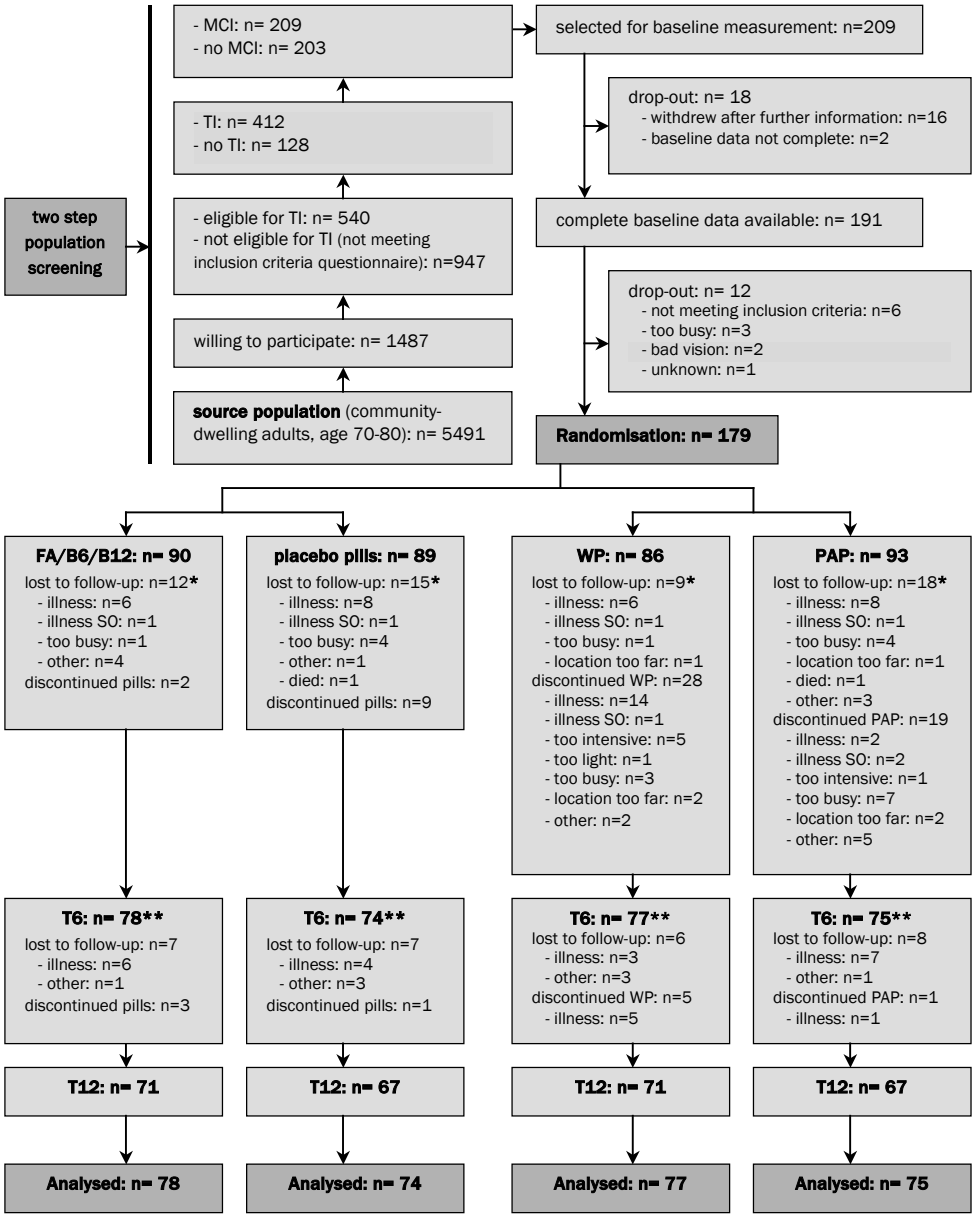


FIGURE 1: Flow chart

TI= Telephone Interview; MCI= Mild Cognitive Impairment; FA/B12/B6= Folic Acid, vitamins B12 and B6; WP= Walking Program; PAP= Placebo Activity Program; SO= Significant Other; T6= Follow-up after 6 months; T12= Follow-up after 12 months; * Excluded from analysis (only baseline data); ** Included in analysis

TABLE 2: Baseline characteristics of participants (n= 152)

	Vitamin intervention		Exercise intervention	
	FA/B12/B6 (n= 78)	Placebo (n= 74)	WP (n= 77)	PAP (n= 75)
Age (Mean (SD))	75 (2.8)	75 (2.9)	75 (2.9)	75 (2.8)
Gender (% male)	56	55	48*	64
MMSE (Median (25^{th}; 75^{th} ‰))	29 (28; 29)	29 (28; 29)	29 (28; 29)	29 (28; 29)
AVLT delayed recall	5.9 (2.6)	5.7 (2.3)	6.1 (2.5)	5.6 (2.3)
Education (% low/intermediate/high)[a]	57/26/17	55/26/19	61/22/17	52/29/19
Marital status (% living with partner)	69	73	75	68
PA, min/day (Median (25^{th}; 75^{th} ‰))[b]	72 (43; 108)	64 (33; 89)	71 (43; 88)	67 (36; 124)
Blood pressure (% hypertension)[c]	25	16	27*	14
BMI, kg/m2 (Median (25^{th}; 75^{th} p‰))	26.5 (24.6; 29.8)	26.7 (24.4; 29.2)	26.7 (24.0; 28.8)	26.6 (24.8; 30.0)

FA/B12/B6= folic acid, vitamins B12 and B6; WP= walking program; PAP= placebo activity program; MMSE= Mini Mental State Examination; AVLT= Auditory Verbal Learning Test; PA= Physical Activity; BMI= Body Mass Index; [a] *low*= no education, primary education, lower vocational training, *intermediate*= intermediate level secondary education, intermediate vocational training, *high*= higher level secondary education, higher vocational training, university training; [b] ≥ 3.0 Metabolic Equivalents; [c] Hypertension= diastole ≥ 90 and systole ≥ 160; * Significantly different from PAP ($p<0.05$)

Blood

Tables 3a and 3b show the median concentrations of the biochemical variables at baseline and after six and 12 months intervention, and the prevalence of hyperhomocysteinemia and vitamin B deficiencies. About a quarter of the population had baseline concentrations of homocysteine above the reference value of 14 micromol/liter. In the FA/B12/B6 group, the prevalence of hyperhomocysteinemia decreased significantly to four and six percent after six and 12 months respectively, but increased to 39 and 54 percent in the placebo group. At baseline, plasma homocysteine concentrations were moderately inversely correlated with concentrations of serum folate ($r= -0.42$, $p= 0.00$). The inverse correlation between plasma homocysteine concentrations and plasma vitamin B6 ($r= -0.18$, $p= 0.02$) and B12 ($r= -0.15$, $p= 0.06$) was low. There was no correlation between total homocysteine concentration at baseline and minutes per day spent in physical activities of at least moderate intensity ($r= 0.09$, $p= 0.26$).

TABLES 3a and 3b: Median (25th and 75th percentiles) of biochemical variables and percentage of deficiencies at baseline and after six and 12 months - FA/B12/B6 versus placebo and WP versus PAP

3a	FA/B12/B6			Placebo		
	T0 (n= 77)	T6 (n= 78)	T12 (n= 71)	T0 (n= 74)	T6 (n= 74)	T12 (n= 67)
Plasma Hcy	11.1	10.2	10.0	10.4	12.8	14.5
(mmol/L)	(9.2; 13.8)	(8.9; 11.4)*	(8.8; 12.0)*	(9.0; 13.7)	(10.3; 15.7)	(11.8; 17.3)
% HyperHcy	23	4*	6*	23	39	54
Serum folate	17.0	55.0	55.0	17.2	15.5	14.8
(nmol/L)	(13.2; 26.3)	(55.0; 55.0)*	(55.0; 55.0)*	(13.0; 23.1)	(12.5; 22.3)	(11.8; 18.9)
% Folate deficient	1	0	0	1	0	0
Serum B12	257.0	539.0	511.0	243.0	289.0	255.0
(pmol/L)	(207.5; 313.0)	(455.0; 629.0)*	(392.3; 690.8)*	(202.5;298.0)	(234.3; 333.3)	(216.3; 318.0)
% B12 deficient	8	0	0	7	0	5
Plasma B6	76.0	555.0	555.0	72.5	70.0	71.0
(nmol/L)	(57.0; 102.0)	(398.0; 555.0)*	(396.5; 555.0)*	(56.0; 93.3)	(58.0; 84.0)	(61.0; 88.5)
% B6 deficient	0	0	0	0	0	0

3b	Walking Program			Placebo Activity Program		
	T0 (n= 77)	T6 (n= 77)	T12 (n= 71)	T0 (n= 75)	T6 (n= 75)	T12 (n= 67)
Plasma Hcy	11.1	10.9	11.0	11.2	10.9	12.1
(mmol/L)	(9.2; 13.8)	(9.4; 13.3)	(9.6; 14.9)	(9.0; 14.3)	(9.8; 13.5)	(10.4; 15.1)
% HyperHcy	23	20	28	27	20	31
Serum folate	17.0	55.0	55.0	16.7	55.0	25.0
(nmol/L)	(13.2; 26.3)	(17.4; 55.0)	(15.6; 55.0)	(13.0; 21.5)	(15.1; 55.0)	(12.9; 55.0)
% Folate deficient	1	0	0	0	0	0
Serum B12	257.0	450.0	353.5	247.5	398.5	344.5
(pmol/L)	(207.5; 313.0)	(296.5; 546.0)	(251.8; 520.0)	(193.0; 295.0)	(266.8; 571.5)	(239.0; 519.0)
% B12 deficient	8	0	2	8	0	3
Plasma B6	76.0	251.0	216.0	64.0	187.0	120.0
(nmol/L)	(57.0; 102.0)	(69.8; 555.0)	(71.0; 555.0)	(53.0; 85.0)	(72.5; 555.0)	(68.0; 555.0)
% B6 deficient	0	0	0	0	0	0

FA/B12/B6= Folic acid, vitamins B12 and B6; Hcy= Homocysteine; * p<0.05 (difference between FA/B12/B6 and placebo)

The effect of the FA/B12/B6 and the WP on the plasma homocysteine concentrations is reported in Table 4. After adjusting for the baseline homocysteine concentration, age and gender, a significant difference in change in homocysteine concentrations was observed between vitamin supplementation and placebo (adjusted difference [95% CI]= -3.7 [-4.5; -3.0] and –4.9 [-5.7; -4.0] micromol/liter after six and 12 months follow-up respectively). Differences between the WP and the PAP were not significant (adjusted difference [95% CI]= -0.2 [-0.9; 0.6] and –0.6 [-1.4; 0.3] micromol/liter after six and 12 months follow-up respectively).

TABLE 4: Differences between baseline and six months, and baseline and 12 months – FA/B12/B6 versus placebo and WP versus PAP

	FA/B12/B6 vs. placebo Beta (95%CI)	p-value	WP vs. PAP Beta (95%CI)	p-value
plasma homocysteine (mmol/L) baseline – 6 months				
crude[a]	-3.7 (-4.5; -3.0)	0.00	-0.3 (-1.0; 0.4)	0.42
adjusted[b]	-3.7 (-4.5; -3.0)	0.00	-0.2 (-0.9; 0.6)	0.66
plasma homocysteine (mmol/L) baseline – 12 months				
crude[a]	-4.9 (-5.7; -4.1)	0.00	-0.6 (-1.5; 0.2)	0.13
adjusted[b]	-4.9 (-5.7; -4.0)	0.00	-0.6 (-1.4; 0.3)	0.17

FA/B12/B6= Folic Acid, vitamins B12 and B6; WP= Walking Program; PAP= Placebo Activity Program; [a] Covariates: baseline homocysteine concentration, vitamin and exercise intervention; [b] Adjusted for: baseline homocysteine concentration, vitamin and exercise intervention, gender, age, if applicable: session attendance

DISCUSSION

This randomised controlled trial demonstrates that 12 months of supplementation with folic acid, vitamin B12 and vitamin B6 is effective for improving homocysteine concentrations in older adults with mild cognitive impairment. No significant effect was observed with 12 months participation in our moderate intensity walking program.

At baseline, the prevalence of hyperhomocysteinemia in our study was about 25 percent. Quadri et al. (2004) reported a higher prevalence of hyperhomocysteinemia (42%) within a population of people with MCI.[9] In the trial of de Jong et al. (2001) among community-dwelling frail older adults (mean age 78 years), one-half of the study population had baseline concentrations of homocysteine above the reference value (16.2 micromol/liter).[18] A possible explanation is the use of different laboratory methods and cutt-offs. In the vitamin supplementation group, prevalence of hyperhomocysteinemia decreased to six percent after 12 months intervention, while in the placebo vitamin groups the prevalence increased further to 54 percent. This is a remarkable finding, since there were hardly any individuals with below normal vitamin B6, B12 or folate concentrations, neither at baseline nor at follow up at six and 12 months. This is in concordance with other studies that found that vitamin B deficiency is common among older adults, even in the presence of normal serum vitamin concentrations.[11,13]

Our results regarding folic acid, vitamin B12 and vitamin B6 supplementation are consistent with the effects observed in other populations with MCI.[10] To our knowledge, this study is the first randomised controlled trial that examined the effect of physical exercise on homocysteine concentrations in participants with MCI. No significant difference between the moderate intensity walking program and the low intensity activity program was observed. However, the between group difference was in the expected direction and increased with the duration of the intervention (between group difference [95% CI]= -0.2 [-0.9; 0.6] micromol/liter after six months follow-up to -0.6 [-1.4; 0.3] micromol/liter after 12 months follow-up). Thus, the intervention duration may not have been long enough. The long-term effects of this type of intervention should be examined in future studies. Another possibility may be that the walking program was not intensive enough.

Our findings have some limitations. One issue is the generalizability of our findings. Although we included participants with MCI from the community, our findings may not apply to older adults with a clinical diagnosis of MCI or those with more severe cognitive impairments. Another point is the moderate adherence to the exercise sessions that may have contributed to the lack of a significant exercise effect. A strength of this study is its design. Participants were randomly assigned to the intervention groups and both participants as well as exercise trainers and outcome assessors were blinded to group allocation. Furthermore, the data were analysed according to the intention-to-treat principle including all randomised participants with available data irrespective of compliance with the protocol.

Both interventions were generally well tolerated. Compliance with vitamin supplementation was almost 100 percent. Only two participants stopped taking vitamin pills after reporting sleep problems and increased forgetfulness; one participant discontinued the placebo-pills after reporting not feeling well. Median session attendance during the total intervention period was, however, only 51 percent at the walking program and 53 percent at the placebo activity program. Importantly, MCI did not interfere with the ability to participate in the walking program, and a positive effect was observed on aerobic fitness in participants who attended the walking sessions regularly. No adverse events of the walking program or placebo activity program were reported.

In summary, the present study demonstrated that 12 months of folic acid, vitamin B12 and vitamin B6 supplementation significantly improved homocysteine concentrations in older adults with mild cognitive impairment, while 12 months moderate intensity walking did not.

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6

General Discussion

This thesis describes the results of a randomised controlled trial (RCT) on the effectiveness of moderate intensity aerobic exercise and vitamin B supplementation in community dwelling adults with mild cognitive impairment (MCI): Project FACT (Folate physical Activity Cognition Trial). The main outcome measure was cognitive function, which was assessed by a number of neuropsychological tests measuring various aspects of cognition. Secondary outcomes were quality of life, habitual physical activity levels, aerobic fitness and homocysteine and vitamin B concentrations. In this Chapter the main findings of Project FACT are summarised. Moreover, the strengths and limitations and general methodological considerations are discussed, followed by public health implications and recommendations for future research. The Chapter ends with the final conclusions.

Main findings

Selecting subjects with MCI from the general population

MCI is a potential transitional stage between normal ageing and dementia. To date however, the concept of MCI has not been well defined. As the concept of MCI is derived from a clinical setting, selecting subjects with MCI from the general population for epidemiological research is complicated. As a compromise between in-depth clinical neuropsychological assessment and a brief assessment using screening measures of cognition, a two step population screening tool, involving a postal questionnaire and telephone interview, was developed to select older adults with MCI from the general population. In this screening, the five criteria for MCI as proposed by Petersen (1999) were assessed: 1) memory complaints; 2) impaired memory; 3) normal general cognitive function; 4) normal daily function; 5) not demented. The postal questionnaire included questions about memory complaints and daily function. The telephone interview included the 'telephone interview for cognitive status' to assess general cognitive function and the 'ten word learning test' in which immediate recall (three trials) and delayed recall were measured to asses memory. This screening by questionnaire and telephone was compared with a subsequent face-to-face interview in which in-depth neuropsychological assessment was made. The percentage agreement between the two-step population screening and the subsequent face-to-face interview was 41 percent, indicating that the two step population screening was able to detect a considerable number of subjects defined as having MCI, according to in-depth neuropsychological assessment.

Effectiveness of exercise and vitamin B supplementation

Moderate intensity walking

The moderate intensity walking program did not prove effective in improving cognitive function or quality of life in the intention-to-treat analysis. However, for some of the outcome measures for cognition and quality of life, there was an interaction between session attendance and the walking program. With increasing session attendance, significant improvements were observed in the following measures: memory and attention in women (0.04 words (Auditory Verbal Learning Test, delayed recall) and 0.3 seconds (Stroop Colour Word Test-Abridged) per percent increase in session attendance), self rated mental health in men (0.03 points per percent increase in session attendance), and feelings of belonging and positive affect in both men and women (0.003 and 0.002 points per percent increase in session attendance respectively). In the per protocol analysis, including participants who attended at least 75 percent of the sessions, a positive effect of moderate intensity walking was observed on memory in men (difference [95 percent confidence interval]= 1.5 [0.1; 3.0] words). In both men and women, the walking program also had small but significant beneficial effects on positive affect (difference [95 percent confidence interval]= 0.23 [0.06; 0.39] points) and self esteem (difference [95 percent confidence interval]= 0.17 [0.001; 0.34] points).

Vitamin B supplementation

In the intention-to-treat analysis, a beneficial effect of vitamin B supplementation was only observed on information processing in women, as measured by the Digit Symbol Substitution Test (difference [95 percent confidence interval]: 2.9 [0.6; 5.3] symbols).

Interaction between walking and vitamin supplementation

Even though it was assumed that both interventions were independent, the possibility of interaction between the walking program and vitamin supplementation was assessed in the analyses of the 17 outcome measures (Chapter 5.1 'cognition': eight outcome measures; Chapter 5.2 'quality of life': seven outcome measures; and Chapter 5.4 'homocysteine concentrations': two outcome measures). In concordance with expectations, no significant interaction was observed in the majority of the analyses (i.e. 15 out of 17). However, in two cases, both cognitive outcome measures, the interaction was significant ($p < 0.10$). It must be noted that the RCT was not powered to examine interaction effects. Based on the a priori assumption of independent interventions, analyses were conducted according to factor, i.e. walking program versus placebo activity program and vitamin supplementation versus placebo.

Feasibility

Vitamin supplementation significantly decreased plasma homocysteine concentrations. In participants in the intervention group with hyperhomocysteinemia at baseline, homocysteine concentrations normalised within six months. The feasibility of vitamin supplementation in this study population appeared to be very good. Compliance with taking the pills was almost optimal, as determined on the basis of pill counts in retrieved blister packs, and blood vitamin and homocysteine concentrations. Only very few participants (3 out of 152) discontinued the vitamin or placebo supplementation after experiencing adverse side effects. Two participants stopped taking vitamin pills after reporting sleep problems and increased forgetfulness; one participant discontinued the placebo-pills after reporting not feeling well. Thus, it can be concluded that vitamin supplements were well tolerated in this population.

There was a significant improvement in aerobic fitness in participants in the walking program, compared with participants in the placebo activity program (difference [95 percent confidence interval]: 71.4 [8.3; 136.1] metres). The feasibility of the exercise programs was determined in terms of session attendance and compliance with intended exercise intensity. Exercise intensity in the walking program was significantly higher than in the placebo activity program. On average, the actual exercise intensity of both programs was as intended, i.e. moderate in the walking program and low in the placebo activity program. No adverse events of the exercise programs were reported. In participants who started the programs, attendance was good (median 71 percent, interquartile range 41-83 percent) and comparable with other exercise intervention studies in older adults. However, it should be noted that a substantial number of participants did not attend a single session (30 out of 152), or discontinued after only one or two sessions.

In conclusion, the moderate intensity walking program induced some beneficial effects on cognitive function (memory and attention in women and memory in men) and quality of life in community-dwelling older adults with MCI who attended the walking sessions regularly. Moreover, a positive effect on aerobic fitness was observed. One significant difference in cognition (information processing in women) and no differences in quality of life outcomes were observed between the vitamin supplementation and placebo supplementation groups. Vitamin supplementation did, however, result in decreased homocysteine concentrations.

Strengths and limitations

Exercise programs

A particular strength of this RCT was the inclusion of a low intensity placebo activity program. Previous studies on the effect of exercise on cognition have often included a non-intervention control group (see Chapter 2). Inclusion of a proper control intervention improves the methodological quality of a trial, so that the Hawthorn effect of attention can be excluded.

It is not likely that participants in the RCT could tell the difference between the intervention and control program, since both exercise programs were based on existing exercise programs in The Netherlands. The low intensity placebo activity program mainly consisted of aspects of programs which are widely available to older adults, for example balance training, tai chi and yoga, and exercises for improving posture during Activities of Daily Living. The walking program was based on Sportive Walking, a moderate intensity aerobic training program. Sportive Walking is not specifically promoted for older adults, but in older age groups, walking is a particularly suitable method for improving aerobic fitness. Another advantage of making use of existing exercise programs is that both programs were feasible for older adults in terms of specific program content and intensity.

The study described in this thesis targeted subjects with MCI. Cognitive status of the participants was taken into account, to the extent of informing instructors to give clear instructions, and to explain these patiently if not understood by the participants. The concept of MCI implies after all that general cognitive function is preserved and that memory impairment does not interfere with Activities of Daily Living.[1] Therefore, the cognitive status of this community dwelling study population was not expected to impede participation in the exercise programs. Indeed, the few participants who were diagnosed with dementia during the RCT continued participation in the exercise programs.

The intensity of the placebo activity program was intended to remain low during all sessions. In the development of the walking program, much attention was paid to establish gradually increasing intensity in each session and during the whole program. A limitation of the RCT was that it was not possible, for practical and logistical reasons, to record heart rate in order to measure exercise intensity objectively during all sessions in all groups. Instead, intensity was monitored subjectively during the classes by the instructors. Furthermore, participants were taught to monitor exercise intensity themselves by focusing on physical responses in relation to the intended intensity of the program. In the evaluation of the

program intensity (Chapter 5.3), this appeared to be a feasible method. However, standardised heart rate recordings during all sessions would have provided a better insight into actual intensity for exercise instructors, participants and researchers.

Vitamin B supplementation

A strength of this RCT is that the vitamin supplements are available on prescription in The Netherlands. They contain a combination of high doses of B vitamins, i.e. 5 milligrams folic acid, 0.4 milligrams vitamin B12 and 50 milligrams vitamin B6. The supplements are prescribed for older adults with memory complaints and white matter atrophy or women who are pregnant with more than one foetus. The advantage of using an existing supplement is that it is readily available if proven effective.

The extremely high doses of B vitamins may, however, be considered as a limitation, even though it is common practice that subjects use these supplements for long periods. It was important, however, to avoid adverse side effects to prevent potential drop out from the trial. Therefore, an authority in the field of homocysteine and B vitamins was consulted before the start of the trial. He confirmed that it was not likely that providing high dose vitamin B supplementation for twelve months would result in side effects in the study population. Since B vitamins are water soluble, any surplus is excreted through urine.

Methodological considerations

Many of the methodological strengths and limitations of the RCT have already been elaborated upon in the articles presented in this thesis. However, some general methodological issues are discussed in more depth here.

Measurement issues

Outcome assessment

Cognitive function, quality of life and habitual physical activity level were assessed during a personal interview at baseline and after six and twelve months. The interview lasted approximately ninety minutes, including a break. Potential learning effects with respect to content of the tests were minimised using parallel tests during the follow-up measurements. Interviews were administered by research assistants blinded to treatment allocation of the study participants. All research assistants took part in a training program before the start of the measurement periods, in which they were taught to follow a standardised protocol. This was done in order to optimise comparability between research assistants and minimise measurement error.

It is important that the measurement burden should be acceptable for the participants. Since cognitive testing may be considered demanding by adults with MCI, cognitive outcomes were gathered in a limited number of tests and in limited time, to enable participants to maintain concentration for each test. Cognitive function was measured using five objective cognitive tests which assessed different domains of cognition, i.e. Mini Mental State Examination (MMSE), Auditory Verbal Learning Test (AVLT), Abridged Stroop Colour Word Test, Digit Symbol Substitution Test and Verbal Fluency Test. In the measurement protocol, 40 minutes were assigned for completion of these neuropsychological tests. To ensure that participants put their best effort into each test, they had a short break after finishing the MMSE and AVLT, or whenever they requested a break. All the 179 participants who were tested at baseline finished the neuropsychological tests within the assigned time span. This indicates that the neuropsychological tests conducted in the trial were suitable and well accepted by the participants.

Measurement Instruments

Two fundamental criteria for judging the quality of measurement instruments are validity and reliability. Validity refers to the issue of whether or not a test measures what it purports to measure. Reliability is a measure of the consistency of the test results. Only measures with good validity and reliability properties were selected to assess outcomes in this RCT. Cognitive function was measured using five tests that are frequently used for both clinical and research purposes in older populations. Quality of life and physical activity level were assessed using measures that are primarily used for research purposes.

Another important methodological consideration in the choice of outcome measures was population specificity. To our knowledge no cognitive tests have been designed specifically for people with MCI. While existing tests are suitable for assessing cognitive function in this population, it is important to pay attention to floor and ceiling effects. Since participants in the present RCT reported memory complaints and were interested in participating in an RCT on cognitive decline, it is likely that they were concerned about their cognitive status. The cognitive tests should therefore be chosen with care. If the tests are too simple, a ceiling effect may exist and participants may have the feeling that their complaints are not taken seriously. If the tests are too demanding, a floor effect may occur and subjects may feel confirmed in their worries, which in turn may negatively affect their performance on other tests. The first case was illustrated by the assessment of the MMSE. To make people feel at ease, the MMSE was assessed first, because it is a relatively simple test. However, many participants were annoyed by the kind of questions in the MMSE. For one subject, this was the reason for withdrawing from further participation. On the other hand, the AVLT appeared

to be too demanding for two participants, who discontinued the baseline measurement during this test. To avoid such reactions, it is important to explain the purpose of the individual neuropsychological tests very carefully. Since measures used to assess quality of life and physical activity level were designed for use in older populations, it is unlikely that population specificity was a matter of concern for these outcomes

Finally, responsiveness to change was a test characteristic that was taken into account for the choice of outcome measures. The cognitive tests used in the RCT are commonly used for clinical purposes to monitor the course of cognitive decline over time. They have shown to be responsive to change in previous studies on the effects of physical activity and exercise, and on the effects of vitamin B supplementation on cognition.

The possibility that quality of life represents a stable concept which is difficult to change has been discussed before.[2] This may originate from the psychological mechanism called adaptation, which has also been referred to as response-shift.[3] Even though the majority of older adults are confronted with mental and physical decline, quality of life measures may not be responsive to change, as ageing subjects may adapt to decline in functions. It is also possible that subjects adapt to improvements, making small improvements indistinguishable. Indeed, quality of life ratings hardly changed, neither in the intervention nor in the control groups.

Since data on physical activity obtained from questionnaires have limited reliability and validity[4], physical activity questionnaires may be more suitable for classifying physical activity than for assessing changes over time within subjects. Therefore, it was intended to collect objective physical activity data among a subgroup of participants using accelerometers. Unfortunately, only a small number of accelerometers was available for the RCT, eight for participants in the walking program and eight for participants in the placebo activity program. Due to dysfunction of a few accelerometers and the fact that not all sixteen participants wore them correctly, the amount of valid accelerometer data was insufficient to provide useful information.

Statistical issues

Randomisation

The aim of randomisation is to distribute participants with different characteristics and levels of performance in both measured and unmeasured variables evenly across intervention groups. In this RCT, randomisation was stratified for self-reported physical activity level, to ensure an equal distribution of inactive and active participants into the exercise intervention groups. Physical activity level was determined using the LASA physical activity questionnaire, a valid and reliable instrument for classifying physical activity in older Dutch adults.[5] Despite randomisation, the proportion of men in the placebo activity program was significantly higher than the proportion of men in the walking program. Therefore, gender was added as a covariate in the analysis. Moreover, for all outcome measures, interaction between the interventions and gender was checked, and analyses were stratified for gender in cases of significant interaction.

Modified intention-to-treat analysis

An intention-to-treat analysis provides optimal information about the effectiveness of an intervention, since data from all randomised subjects are included in the analysis. However, it is very difficult to create a complete data set in epidemiological research. Even though all randomised participants were sent a postal invitation for the follow-up measurements and non-responders were contacted twice by phone, 27 out of 179 participants did not comply with our invitation for several reasons (e.g. not wanting to participate after all, not being able to attend due to illness).

A common approach in the case of missing data in longitudinal studies is imputation. Imputation methods in longitudinal data analysis include 'last value carried forward', 'linear interpolation' or 'longitudinal regression'.[6] In the first method, the baseline value would have been imputated in both follow-up measurements. The opinion 'last value carried forward' and imputation of two values on the basis of only one available value, was considered to be inappropriate because cognitive performance may vary in subjects with MCI. 'Linear interpolation' and 'longitudinal regression' assume a linear development of the variable over time, and therefore require data at the time point before and the time point after the missing value. Thus, these methods were not applicable either. Therefore, the 27 participants who only provided baseline data could not be included in the analysis. Moreover, Twisk (2003) states that in the case of multilevel analysis, it may be better to use no imputation at all and to analyse longitudinal data sets with missing data. According to Twisk (2003) the results of multilevel analysis performed on datasets with missing data are comparable to the results obtained from complete datasets.[6]

Premature drop-out may complicate the unbiased comparison of interventions. This is in particular the case if the participants who discontinued differ from those who remain with respect to the main outcome variables. Twenty-three of the 27 participants who only provided data at baseline did not start taking the (vitamin) pills and 14 of them did not participate at all in the exercise interventions. Median adherence to the exercise programs in the other seven was only seven percent. It is therefore clear that this group did not comply well with the interventions. The 27 participants who only provided baseline data and the participants who provided data at at least one follow-up measure did not differ with respect to general cognitive function and specific cognitive functions. Moreover, baseline comparisons only revealed differences in marital and smoking status. It is not likely that these differences promoted early drop-out.

Data from 152 participants who provided data at baseline and at at least one follow-up measurement were included in the analysis. This population included both those who finished the interventions and those who discontinued the interventions but participated in the follow-up measurements. To indicate that we were not able to follow-up all randomised participants, but included data from participants who discontinued the interventions, we refer to the analyses as modified intention-to-treat analyses.

Secondary analysis

A 'per protocol analysis' was performed in a subgroup of the total study population who attended at least 75 percent of the exercise sessions. The strength of evidence for subgroup effects depends on the question of whether hypotheses have been defined prior to the analysis and whether there is biological plausibility of the effects.[7] In this RCT, it was hypothesised that moderate intensity walking would benefit cognitive function via the assumed biological mechanism of improving aerobic fitness. It is however biologically plausible that aerobic fitness would only improve in those participants who regularly participated in the moderate intensity walking sessions. It is unlikely that only participants without progressive MCI were included in the per protocol analysis, since session attendance was not significantly correlated with any of the cognitive outcomes assessed at baseline.

A potential problem regarding the statistical issues, which applies to our per protocol analysis, is the performance of multiple comparisons. Multiple comparisons result in an increased likelihood of finding significant differences by chance. No correction was made for performing multiple comparisons in the analysis for the present RCT, since these corrections are not essential in the case of testing plausible and a priori defined hypotheses.[7]

Generalizability

The method of recruiting study participants by sending an invitation letter and information brochure to all community-dwelling older adults aged 70-80 years probably resulted in some volunteer bias. Previous research in The Netherlands has shown that older adults participating in an exercise intervention were younger, better educated, had better physical function and (Instrumental) Activities of Daily Living and were more physically active than subjects who did not participate.[8] As in the present RCT, subjects in that study were recruited by means of a postal invitation and brochure, so that volunteer bias presumably limits the generalizability of results to the elderly population in general.

A more specific issue with respect to generalizability is the operationalisation of the concept of MCI. MCI originates from a clinical setting, in which the fulfilment of criteria is determined through clinical judgment after clinical examination, including in depth neuropsychological testing.[9] This is not feasible in most epidemiological studies because of financial and time constraints. Furthermore, no consensus exists on the number and content of the neuropsychological tests required to assess memory function, or on how many standard deviations below the norm should be considered 'impairment'.[10] In the present RCT, the ten word verbal learning test was used to assess memory. In previous epidemiological studies[11,12], a cut-off point of one standard deviation below the mean of delayed recall has been used to recruit a sufficient number of participants. However, according to the Petersen criteria, memory performance of clinical MCI populations is defined at one-and-a-half standard deviations below the mean.[1] Consequently, the characterisation of subjects with MCI is likely to differ between MCI populations in epidemiological research and clinical populations.[13] Therefore, the results of this RCT may be generalizable to community-dwelling older adults with memory complaints in general, but probably less generalizable to subjects with clinical MCI.

Furthermore, only participants who reported being able to participate in moderate intensity physical activity were eligible for inclusion in the trial. This may limit generalisation of the results to all community-dwelling older adults with MCI as well. It was initially intended to only include those who reported being moderately physically active for one hour or less per week. Unfortunately, this intention seriously limited the number of eligible participants, so that participants were included irrespective of self-reported physical activity levels. Therefore, even though participants may have been relatively healthy and physically active at baseline, beneficial effects of moderate intensity walking exercise on cognition and quality of life were found in those who attended the sessions regularly. However, it has been established that the largest effects of exercise on cognition in cognitively healthy elderly are

to be expected in the sedentary elderly.[14] Therefore, it could be assumed that older adults with MCI who are less physically active would benefit more from the walking intervention.

In the per protocol analysis, several beneficial effects of the walking program were observed on cognition and quality of life in those who attended the exercise sessions regularly. The drawbacks of subgroup analyses have already been discussed in the previous section entitled 'secondary analyses'. With respect to generalizability of these results, it must therefore be kept in mind that 'per protocol analysis' and analysis of interactions between the walking program and session attendance provide limited information about the effects of the interventions in this population of community dwelling older people with MCI.

Public health implications

Cognitive decline is an important public health issue since the number of older adults is still increasing and the majority of these adults will be confronted with some deterioration in cognitive function. To a certain extent, cognitive decline is a direct consequence of ageing. However, a decline in memory in particular may represent an abnormal course, finally leading to Alzheimer's disease. Thus, memory complaints reported by the older adults themselves, or noticed by their significant others, general practitioner or other caregivers, have to be taken seriously.[15] If serious cognitive decline is suspected, cognitive function should be monitored and recorded over time, in order to be able to confirm or refute the suspicions.

The prognosis is that the number of older adults with late onset dementia in The Netherlands will increase from 207,000 in 2010 to 412,000 in 2050.[16] Therefore, even small benefits may have large implications for public health. Unfortunately, no consistent beneficial effects of vitamin B supplementation on cognition were shown in the present RCT among community-dwelling elderly with MCI. On the basis of the results of the RCT, high dose vitamin B supplementation should not be recommended yet for improvement of cognition among older adults with mild cognitive impairment.

A positive effect was observed on aerobic fitness in participants who attended the walking sessions regularly. Only in the subgroup of the population who exercised regularly, some beneficial effects of the walking program on several cognitive outcomes, including memory, were observed. Therefore, from the viewpoint of public health, regular participation in moderate intensity physical activity should be promoted to older adults. This is already the case since, according to the Dutch physical activity guidelines, adults aged 55 years or older

are recommended to be physically active at moderate intensity for 30 minutes or more on at least five, but preferably all, days of the week.[17] Nonetheless, a considerable proportion of older adults may not understand what is meant exactly by moderate intensity physical activity. A good understanding of this concept is very important, since moderate intensity physical activity is known to generate many health benefits.[18] Study participants were taught about the physiological effects of moderate intensity exercise, such as increased breathing frequency, turning red and transpiration. Objective heart rate recordings confirmed that this was a feasible method for the elderly to monitor their exercise intensity. Translating this information to a public health setting could mean that compliance with current physical activity guidelines at the population level may be enhanced by making older adults aware of physiological effects of moderate intensity physical activity.

In The Netherlands, various exercise programs are already available for older adults. However, the intensity of most programs targeting older adults is low. Potential reasons are that individuals themselves are not used to moderate intensity physical activity. Presumably, the exercise instructors may also be cautious regarding increasing exercise intensity. Therefore, it is important to deal with the advantages of moderate intensity exercise in the education of exercise instructors for the elderly. Moreover, during their education they should be provided with tools for helping to make older adults aware of exercise intensity.

To conclude, in order to encourage older adults to be physically active, appropriate moderate intensity aerobic exercise programs should be made readily available to people with different levels of cognitive and physical function. In order to bring about public health benefits of improved aerobic fitness among older adults, health care insurance packages could include compensation for costs related to participation in exercise (i.e. 'prescribe exercise') which is designed to improve aerobic fitness, and physical fitness in general.

Future research

The use of different operationalisations for the criteria of mild cognitive impairment complicates comparisons between epidemiological studies. Future research should therefore include the development of adequate definitions and operationalisations of MCI, in order to recruit comparable study populations. Without this, the cognitive characteristics of recruited study populations should be described extensively in order to correctly assess the cognitive status of particular study populations along the spectrum of cognitive decline.

With respect to vitamin B supplementation, results are mixed. In the most recent systematic review, including 14 randomised controlled trials, it was concluded that there is no adequate evidence for an effect of vitamin B6, B12, or folic acid, alone or in combination on cognitive function in older adults.[19] However, significant beneficial effects on cognitive function were recently observed after three years of vitamin B supplementation.[20] More long term supplementation trials are needed to replicate these findings. For this reason, the vitamin B supplementation intervention of Project FACT has now been extended for three years and will last to 2008. The extension study is called the Longitudinal Assessment of MCI in Alkmaar (LAMA).

From the systematic review on exercise programs for older adults with different levels of cognitive function (see Chapter 2), it was concluded that most existing trials were of low methodological quality. Several recent studies did not perform, or mention, blinding of participants, exercise instructors and outcome assessors. Also, in most studies data were not analysed according to the intention-to-treat-principle. Furthermore, in the majority of previous trials, data were analysed using techniques which do not provide information about the direction and the precision of between group differences. Well designed randomised controlled trials, with intention-to-treat analysis and using sophisticated techniques to analyse data, would improve insight in the effectiveness of exercise on cognitive function.

Future studies should also focus on determinants of drop-out from the exercise programs and whether these are correlated with cognitive status. Such information would be very useful in the development of future exercise intervention trials in older adults with cognitive decline. This information would enable researchers to anticipate drop-out and develop methods for encouraging participants to comply with and remain in the program.

Particularly for a population with MCI, the follow-up duration of one year may have been too short to demonstrate consistent effects on cognition. From the literature it is known that 80 percent of subjects with MCI will develop dementia within five years.[1] Hypothesised precursors of changes in cognitive function, i.e. cerebrovascular quality and integrity, neurotransmitter function, neuro-endocrine function and brain morphology, may need more time to consolidate. Thus longer term intervention studies, including firm outcomes such as conversion to dementia, as well as measures of the hypothesised mechanisms, would increase knowledge. An important draw-back of such longer term interventions would however be the potential bias as a result of selective loss to follow-up.

Final conclusions

The moderate intensity aerobic walking program and vitamin B supplementation positively affected the mechanisms by which they were hypothesised to benefit cognitive function. Aerobic fitness improved and homocysteine concentrations decreased.

Both interventions were feasible in this particular population of older community-dwelling adults with mild cognitive impairment. Session attendance in participants who started the exercise programs was good and exercise intensity commensurated with intended intensity. Cognitive status did not interfere with the ability to participate. Compliance with taking the (vitamin) pills was almost optimal.

However, no effects of vitamin supplementation were observed on measures of cognition, except for a beneficial effect on information processing in women, and quality of life within one year. Since compliance with vitamin supplementation approached 100 percent, on the basis of this randomised controlled trial it can be concluded that one year of vitamin B supplementation was not effective in improving cognition or quality of life in older community-dwelling adults with mild cognitive impairment.

Moreover, there were no main effects of the aerobic walking program in the modified intention-to-treat analysis. Unfortunately, average session attendance was only moderate since a proportion of participants attended no sessions at all, or only few. However, memory and attention appeared to improve with increasing session attendance in women. This was also the case for some aspects of quality of life in both men and women. Furthermore, in the per protocol analysis in participants attending at least 75 percent of the sessions, a beneficial effect of aerobic exercise was observed on memory in men and on positive affect and self-esteem in both men and women.

On the basis of these results, it cannot be concluded that the moderate intensity aerobic walking program is beneficial for cognitive function in older community-dwelling adults with mild cognitive impairment in general. However, since beneficial effects were observed in the compliant subgroup only, these results provide a basis for a potential beneficial effect of aerobic exercise on cognition and quality of life in community-dwelling older adults with MCI. More high quality studies on this subject are needed. In any event, because of the well-known health benefits of a physically active lifestyle, participation in moderate intensity physical exercise should also be promoted to older people with mild cognitive impairment.

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Summary

We live in a doubly ageing society: not only is the percentage of older adults within the total population growing, the life expectancy of these individuals has also increased. In light of this, the promotion of healthy ageing is becoming more important. Unfortunately, increasing age is accompanied by an increasing risk of age-related health problems, such as cognitive decline and dementia. In The Netherlands, 175,000 adults aged over 65 years suffer from late onset dementia according to 2002 data. Predictions suggest that this number will further increase from 207,000 in 2010 to 412,000 in 2050, if prevalence rates do not change and curative treatments fail to emerge. Alzheimer's disease is the most common cause of dementia, responsible for 72 percent of the cases. In light of the high prevalence of cognitive decline and the growing number of older adults in the population, it is important that strategies for preventing cognitive decline are developed. Prior to a diagnosis of Alzheimer's disease, there is a potential transitional stage, in which persons experience memory loss to a greater extent than expected for age and education, but do not meet the criteria for Alzheimer's disease. This stage is referred to as mild cognitive impairment (MCI). As individuals with MCI have an increased risk of developing dementia, the stage of MCI may be the optimum stage at which to intervene. Chapter 1 explains the concepts of cognition and MCI.

Two potential beneficial interventions for prevention of cognitive decline are physical exercise and vitamin B supplementation. Regular physical exercise results in increased aerobic fitness. Because aerobic fitness is positively related to cognition, improving fitness by aerobic exercise may improve cognition in older adults. Similarly, both normal vitamin B and homocysteine concentrations are positively related to cognition. Because vitamin B supplementation can decrease homocysteine concentrations, this may also help to prevent cognitive decline. The hypothesised mechanisms for the relationship between moderate intensity exercise and B vitamins and cognition are also described in Chapter 1.

The main aim of the work described in this thesis was to examine the effects of moderate intensity aerobic exercise and vitamin B supplementation on cognition in older adults with cognitive decline. In order to do so, a randomised controlled trial was conducted entitled Project FACT: Folate physical Activity Cognition Trial. It was hypothesised that: 1) moderate intensity walking is beneficial for prevention of cognitive decline in community-dwelling older adults with mild cognitive impairment; and 2) supplementation with folic acid, vitamins B12 and B6 is beneficial for prevention of cognitive decline in community-dwelling older adults with MCI. Secondary aims were to address the impact of each intervention on quality of life, aerobic fitness, and homocysteine and vitamin B concentrations.

Chapter 2 includes a systematic review on the effect of physical exercise on cognition in subjects with and without cognitive decline. Twenty-one randomised controlled trials were included in this review. Methodological quality of these RCT's was assessed according to a standardised quality list by two independent reviewers. Moreover, data on study populations, exercise interventions and effectiveness were extracted. Overall quality of the included studies was poor. Only five of the 21 studies were qualified as high quality studies. Fifteen trials were performed among cognitively healthy subjects and six among subjects with cognitive decline. Inconclusive evidence was found for the effect of exercise programs on cognition. Twelve studies, including two in subjects with cognitive decline, found no significant effect of exercise on cognition. Nine studies, including four among subjects with cognitive decline, did observe a beneficial effect of aerobic or strength training on at least one measure of cognition. Observed improvements comprised information processing, executive functions and memory in cognitively healthy adults and global cognitive function and executive functions in adults with cognitive decline. Unfortunately, because of the diversity in exercise programs, measures of cognition, and study populations in included studies, it is impossible to draw valid conclusions about which type of exercise program is most effective, for what aspect of cognition and for which specific population.

Chapter 3 describes the design of Project FACT. Project FACT was developed based on a two-by-two factorial design, with the factors physical exercise and vitamin B supplementation. Study participants were community-dwelling adults with MCI aged 70-80 years, who were able to participate in moderate intensity exercise and who did not use high dose vitamin supplements. After baseline measurements, they were randomly assigned to one year of 1) a twice-weekly, group-based, moderate-intensity aerobic walking program or a low-intensity placebo activity program; and 2) a single daily vitamin pill containing 5 mg folic acid, 0.4 mg vitamin B12 and 50 mg vitamin B6 or a placebo pill. Cognitive function and quality of life were assessed during an interview at baseline and after six and 12 months using neuropsychological tests and questionnaires. Furthermore, blood samples were drawn to determine concentrations of homocysteine and B vitamins. Moreover, during the exercise sessions at the start of the exercise programs and after six and 12 months, heart rate was recorded and subjective intensity was assessed using Borg scales.

Chapter 4 describes the two-step population screening, by questionnaire and telephone, which was designed to recruit subjects with MCI from the general population. In Project FACT, the Petersen criteria for MCI (1999) were used, characterising MCI on the basis of five criteria: 1) subjective memory complaint; 2) memory impairment; 3) normal mental status; 4) intact activities of daily living; and 5) no dementia. Criteria one and four were

addressed in a postal questionnaire, the other three criteria were assessed in a subsequent telephone interview using the Telephone Interview for Cognitive Status and the 10 Word Learning Test. Subjects with MCI according to the two-step population screening were subjected to a subsequent face-to-face assessment, in which cognitive status and memory were assessed using the Mini Mental State Examination (MMSE) and the Auditory Verbal Learning Test (AVLT). Two hundred and twenty-seven subjects completed both the telephone interview and the face-to-face assessment. Ninety three subjects (41 percent) had MCI according to both methods. It was concluded that the two-step population screening was able to detect a considerable number of subjects with MCI in the general population.

Chapter 5 describes the effects of Project FACT on cognitive function, quality of life, aerobic fitness, and homocysteine concentrations. One hundred and seventy-nine subjects were randomised, of which 152 provided data on at least one follow-up measurement. These 152 participants were included in the analysis. Analysis was conducted according to factor, i.e. walking program (n= 77) versus placebo activity program (n= 75), and vitamin B supplementation (n= 78) versus placebo (n= 74).

Chapter 5.1 describes the effects on the primary outcome measure, cognitive function, which was assessed using four neuropsychological tests, i.e. Auditory Verbal Learning Test (immediate + delayed verbal memory), Abridged Stroop Colour Word Test (attention), Digit Symbol Substitution Test (information processing) and Verbal Fluency Test (executive function). The analysis of the cognitive outcome measures was stratified for gender, since there was a significant interaction between the interventions and gender on the majority of the cognitive outcome measure (4 out of 7). Median attendance at the exercise programs (25^{th}; 75^{th} percentile) was 63 (2; 81) percent of the sessions, and median compliance with taking pills (25^{th}; 75^{th} percentile) was 100 (99; 100) percent. A beneficial effect of vitamin B supplementation was only observed on information processing in women, as assessed by the Digit Symbol Substitution Test (between group difference [95 percent confidence interval= 2.9 [0.6; 5.3] symbols). No main effect of walking on cognition was observed within one year in the total population of 152 participants. Unfortunately, 30 of these participants (19 men and 11 women), did not attend a single exercise session but were included in the intention-to-treat analysis. However, with increasing session attendance, significant improvements were observed in memory and attention in women (0.04 words on the Auditory Verbal Learning Test, delayed recall, and 0.3 seconds on the Abridged Stroop Colour Word Test per percent increase in session attendance). Furthermore, in a compliant subgroup of men, attending at least 75 percent of the sessions, a beneficial effect of

moderate intensity walking was observed on memory as assessed with the Auditory Verbal Learning Test, delayed recall (between group difference [95 percent confidence interval]= 1.5 [0.1; 3.0] words).

Chapter 5.2 focuses on the effects of walking and vitamin B supplementation on Quality of Life (QoL). QoL was measured using the population-specific Dementia Quality-of-Life questionnaire (D-QoL) to assess overall QoL and the generic Short-Form 12 mental and physical component scales (SF12-MCS and SF12-PCS) to assess health-related QoL. No beneficial main intervention effect of walking or vitamin supplementation was observed. However, ratings of D-QoL-belonging, D-QoL-positive affect and D-QoL-self esteem subscales improved slightly with increasing attendance at the walking program. Only in men, SF12-MCS ratings improved slightly with increasing session attendance. Though these differences are statistically significant, it can be questioned whether they are clinically relevant.

Chapter 5.3 evaluates the feasibility of the moderate intensity aerobic walking program in terms of session attendance and compliance with the intended exercise intensity, measured using heart rate monitors and Borg scales. Moreover, the effect on aerobic fitness was examined. Median attendance in participants attending at least one exercise session (n= 122) was 70 percent. Session attendance was not related to general cognitive function or memory. Percentage of heart rate reserve and Borg-scale scores were significantly higher in the walking program compared with the placebo activity program and commensurated with moderate intensity. Aerobic fitness, assessed by a sub-maximal walking test, improved significantly in participants who participated in the walking program (between group difference [95 percent confidence interval]= 71.4 [8.3; 136.1] metres, p= 0.03).

Chapter 5.4 describes the effects of supplementation with folic acid, vitamins B12 and B6 and the walking program on homocysteine concentrations. Homocysteine concentrations significantly decreased in the vitamin supplementation group (between group difference [95 percent confidence interval]= -3.7 [-4.5; -3.0] micromol/liter and –4.9 [-5.7; -4.0] micromol/liter respectively, after six and 12 months follow-up). Also, the prevalence of hyperhomocysteinemia decreased significantly in the vitamin group while a significant increase was observed in the placebo group. The walking program was not effective in changing homocysteine concentrations.

In Chapter 6, the main findings are summarised, followed by a discussion of strengths and limitations, general methodological considerations, public health implications, recommendations for future research, and the final conclusions. In conclusion:

- The moderate intensity aerobic walking program and vitamin B supplementation positively affected the mechanisms by which they were hypothesised to benefit cognitive function. Aerobic fitness and homocysteine concentrations improved.

- Both interventions were feasible in this particular population of community-dwelling adults with mild cognitive impairment. Session attendance in participants who started the exercise programs was good and exercise intensity commensurated with intended moderate intensity. Cognitive status did not interfere with the ability to participate. Compliance with taking the (vitamin) pills was almost optimal.

- No effects of vitamin B supplementation were observed on measures of cognition and quality of life within one year, except for a beneficial effect on information processing in women. On the basis of these results, high dose vitamin B supplementation should not yet be recommended for prevention of cognitive decline among older people with mild cognitive impairment.

- In the total study population, there were no beneficial main effects of the aerobic walking program on measures of cognition and quality of life. However, memory and attention appeared to improve with increasing session attendance. This was also the case for some aspects of quality of life (feelings of belonging, positive affect, and self-esteem). Since some beneficial effects were observed in participants who regularly attended the walking sessions, and because of the well-known health benefits of a physically active lifestyle, regular participation in moderate intensity physical activity should be promoted also to older adults with mild cognitive impairment.

Samenvatting

Het percentage ouderen binnen de totale bevolking stijgt, en ook de gemiddelde levensverwachting is toegenomen. Vanwege deze zogenaamde dubbele vergrijzing wordt 'gezond ouder worden' steeds belangrijker. Ouder worden gaat echter gepaard met een toenemend risico op aandoeningen zoals afname van de intellectuele functies (cognitief functioneren) en dementie. In 2002 waren er in Nederland 175.000 mensen van 65 jaar of ouder met dementie. De verwachting is dat, zolang er geen behandeling beschikbaar komt om dementie te genezen, dit aantal zal toenemen van 207.000 in 2010 tot 412.000 in 2050. Omdat cognitieve achteruitgang veel voorkomt bij ouderen en het aantal ouderen binnen de bevolking toeneemt, is het belangrijk om interventies te ontwikkelen om cognitieve achteruitgang te verminderen.

Wanneer er sprake is van geheugenverlies dat ernstiger is dan men op basis van leeftijd en opleiding zou verwachten, maar nog niet zo ernstig dat de diagnose 'dementie' gesteld kan worden, spreekt men van 'mild cognitive impairment' ofwel 'lichte cognitieve stoornis' (LCS). Aangezien ouderen met LCS een hoger risico hebben om dementie te ontwikkelen, lijkt dit de meest geschikte fase om de effecten van mogelijk effectieve interventies te onderzoeken.

Twee mogelijk effectieve interventies voor de preventie van cognitieve achteruitgang zijn lichamelijke activiteit en inname van extra vitamine B. Regelmatige lichamelijke activiteit leidt tot een verbetering van aërobe fitheid. Aërobe fitheid is gerelateerd aan het cognitief functioneren. Daarom zou verbetering van de aërobe fitheid middels conditietraining het cognitief functioneren van ouderen kunnen verbeteren. Inname van extra vitamine B zorgt ervoor dat het gehalte van het aminozuur homocysteïne in het bloed afneemt. Dit zou eveneens het cognitief functioneren kunnen verbeteren, omdat een verhoogd homocysteïne gehalte gerelateerd is aan een verminderd cognitief functioneren.

In dit proefschrift wordt 'Project FACT' beschreven. Project FACT is een onderzoek naar het effect van een wandelprogramma en extra inname van vitamine B op het cognitief functioneren van zelfstandig wonende ouderen met LCS. Behalve de effecten op cognitief functioneren, zijn de effecten op kwaliteit van leven, de aërobe fitheid en het homocysteïne gehalte onderzocht.

Eerst worden de resultaten beschreven van een systematisch literatuuronderzoek naar het effect van beweegprogramma's op het cognitief functioneren van ouderen met en zonder cognitieve stoornissen. Er werden 21 relevante gerandomiseerde en gecontroleerde studies gevonden in de literatuur. De methodologische kwaliteit van deze studies is door twee

onafhankelijke beoordelaars bepaald middels een gestandaardiseerde kwaliteitslijst. De kwaliteit van de studies bleek matig, slechts vijf van de 21 studies kregen het predikaat ‘kwalitatief goed’. Tussen de verschillende studies waren grote verschillen wat betreft de deelnemers, de beweegprogramma’s en de gebruikte cognitietesten. Vijftien interventie studies werden uitgevoerd onder cognitief gezonde ouderen en zes onder ouderen met cognitieve achteruitgang. Het bewijs voor een effect van de beweegprogramma’s op cognitie was niet overtuigend. Er werd geen effect gevonden in 12 studies, waaronder twee onder ouderen met cognitieve achteruitgang. Negen studies, waarvan vier onder ouderen met cognitieve achteruitgang, vonden wel een gunstig effect van conditie- of krachttraining. Bij cognitief gezonde ouderen verbeterden informatieverwerking, vaardigheden om handelingen te overzien, plannen en organiseren en geheugen. Bij ouderen met cognitieve achteruitgang verbeterden vaardigheden om handelingen te overzien, plannen en organiseren en het algeheel cognitief functioneren.

Project FACT werd uitgevoerd in Alkmaar. De deelnemers waren zelfstandig wonende ouderen met LCS tussen de 70 en 80 jaar. De belangrijkste kenmerken waarop de deelnemers werden geselecteerd waren: ‘in staat zijn tot matig intensieve lichamelijke activiteit’ en ‘geen suppletie met hoge doses B vitaminen’.

De deelnemers werden door loting ingedeeld in vier groepen: 1) wandelprogramma en extra vitamine B inname; 2) wandelprogramma en placebo-pillen; 3) controle beweegprogramma en extra vitamine B inname; en 4) controle beweegprogramma en placebo-pillen. Het wandelprogramma was matig intensief en gericht op het verbeteren van de aërobe fitheid en het controle beweegprogramma was licht intensief, met oefeningen voor onder meer lenigheid, balans en houding. Beide beweegprogramma's duurden een jaar. Per week waren er twee sessies van een uur. De extra vitamine B inname bestond uit éénmaal daags een vitamine-pil met 5 mg foliumzuur, 0,4 mg vitamine B12 en 50 mg vitamine B6. Om de effecten van het wandelprogramma te kunnen onderzoeken zijn groepen 1 en 2 (wandelprogramma) vergeleken met de groepen 3 en 4 (controle beweegprogramma). Om de effecten van extra vitamine B inname te onderzoeken zijn de groepen 1 en 3 (vitamine-pillen) vergeleken met de groepen 2 en 4 (placebo-pillen).

Voor aanvang van de interventie en na zes en 12 maanden werd het cognitief functioneren getest en werden de deelnemers geïnterviewd over hun kwaliteit van leven en mate van lichamelijke activiteit. Ook werd er bloed afgenomen om het homocysteïne gehalte te bepalen. Aërobe fitheid is bepaald middels een wandeltest. Om een inschatting te maken van de trainingsintensiteit is gedurende de beweegprogramma’s de hartslag gemeten,

éénmaal in het begin van de interventieperiode, en nog een keer na zes en 12 maanden interventie.

Deelnemers aan Project FACT zijn geselecteerd uit de algehele bevolking. In Project FACT zijn de vijf criteria voor LCS van Petersen (1999) gebruikt: 1) geheugenklachten; 2) geheugen stoornissen; 3) normale mentale status; 4) geen problemen met alledaagse handelingen; 5) geen dementie. Deze vijf criteria zijn gecontroleerd middels een vragenlijst en een telefonisch interview. In september 2003 hebben alle 5491 zelfstandig wonende ouderen in Alkmaar tussen de 70 en 80 jaar per post een FACT vragenlijst ontvangen. Van degenen die aan Project FACT wilden meedoen en aan het eerste en vierde criterium voor LCS voldeden, zijn de overige criteria gecontroleerd in een telefonisch interview. Gedurende dit interview werd een test voor algemeen cognitief functioneren en voor geheugen afgenomen. Ouderen die volgens vragenlijst en telefonisch interview LCS hadden namen vervolgens deel aan een persoonlijk interview, waarbij de cognitieve status en geheugen nogmaals werden onderzocht met uitgebreidere testen. In totaal deden 227 ouderen mee aan zowel de screening per vragenlijst en telefoon, als aan het persoonlijke interview. Drieënnegentig van hen (41 procent) hadden LCS volgens beide methodes. De overige deelnemers (59 procent) hadden alleen LCS volgens de eerste methode. Hieruit kan geconcludeerd worden dat de screening middels vragenlijst en telefonisch interview een aanzienlijk aantal proefpersonen met LCS kan opsporen.

De 152 ouderen die deelnamen aan Project FACT waren als volgt over de interventies verdeeld: wandelprogramma (n= 77) versus controle beweegprogramma (n= 75) en vitamine-pillen (n= 78) versus placebo-pillen (n= 74). De effectiviteit van het wandelprogramma en extra vitamine B inname op cognitief functioneren, kwaliteit van leven, de aërobe fitheid en het homocysteïne gehalte is onderzocht.

Cognitief functioneren is bepaald door vier testen: een test voor geheugen, aandacht, informatieverwerking en vaardigheden om handelingen te overzien, plannen en organiseren. De therapietrouw aan de (vitamine)pillen was zeer hoog (gemiddeld 100 procent). Er werd echter alleen een gunstig effect van extra vitamine B inname gevonden op informatieverwerking bij vrouwen. De therapietrouw aan de beweegprogramma's was lager. De aanwezigheid bij de beweegprogramma's in de hele groep bedroeg 63 procent van alle lessen. Dertig deelnemers waren bij geen enkele les aanwezig. In de totale groep werd geen effect van het wandelprogramma gevonden. Wel ging een toename in aanwezigheid gepaard met een verbetering in geheugen en aandacht bij vrouwen. Bij mannen die meer dan 75 procent van de lessen aanwezig waren (n= 33), was er eveneens een gunstig effect op het geheugen.

In de totale groep hadden het wandelprogramma en extra vitamine B inname geen effect op de kwaliteit van leven. Wel werden ook hier enkele, zeer kleine, verbeteringen gevonden naarmate deelnemers vaker aanwezig waren bij de beweegprogramma's.

De trainingsintensiteit van het wandelprogramma was inderdaad hoger dan die van het controle beweegprogramma en kwam overeen met matige intensiteit. Het wandelprogramma had een gunstig effect op de aërobe fitheid van de deelnemers. De aanwezigheid bij de beweegprogramma's was niet gerelateerd aan het algeheel cognitief functioneren of het geheugen. De gemiddelde aanwezigheid van ouderen die aan de beweegprogramma's deelnamen (n= 122) was goed. Gezien de bereikte trainingsintensiteit, de verbetering van aërobe fitheid en de aanwezigheid van de deelnemers lijkt het matig intensieve wandelprogramma praktisch haalbaar voor zelfstandig wonende ouderen met LCS.

Zoals verwacht was extra vitamine B inname effectief in het verlagen van het homocysteïne gehalte. Het percentage mensen met een te hoog homocysteïne gehalte in het bloed daalde ook in de vitamine B groep, terwijl dit percentage toenam in de groep die placebo-pillen slikte. Het wandelprogramma had geen effect op het homocysteïne gehalte.

Conclusies met betrekking tot de extra vitamine B inname:

- Extra vitamine B inname is effectief in het verlagen van het homocysteïne gehalte in het bloed.
- De therapietrouw van de deelnemers aan de (vitamine) pillen was hoog. Er waren geen noemenswaardige bijwerkingen.
- Extra vitamine B inname was niet effectief in het verbeteren van het cognitief functioneren en de kwaliteit van leven binnen een jaar in de totale groep deelnemers, op een gunstig effect van vitamine B op informatie verwerking bij vrouwen na.
- De resultaten geven geen aanleiding om extra inname van hoge doses vitamine B aan te bevelen voor het verbeteren van cognitie bij zelfstandig wonende ouderen met LCS.

Conclusies met betrekking tot het wandelprogramma:

- Het wandelprogramma had een gunstig effect op de aërobe fitheid.
- Bij de ouderen die deelnamen aan het wandelprogramma, was de aanwezigheid over het algemeen goed. Ook werd de beoogde matig intensieve trainingsintensiteit bereikt.

- Het wandelprogramma was niet effectief in het verbeteren van het cognitief functioneren en de kwaliteit van leven binnen een jaar in de totale groep deelnemers.
- Naarmate de aanwezigheid van deelnemers aan de wandelsessies toenam en in een subgroep van mensen die tenminste 75 procent van de sessies aanwezig was, was wel een verbetering in enkele aspecten van het cognitief functioneren, waaronder geheugen, en kwaliteit van leven te zien.
- Op basis van deze resultaten en gezien de alom bekende gezondheidsvoordelen van een lichamelijk actieve leefstijl, wordt ook aan zelfstandig wonende ouderen met lichte cognitieve stoornissen regelmatige deelname aan matig intensieve lichamelijke activiteit aangeraden.

Curriculum Vitae

Jannique van Uffelen was born on April 18, 1977 in Oldenzaal, The Netherlands. After completing secondary school at the Christelijk Lyceum in Apeldoorn, she studied Exercise Therapy Cesar at the Hogeschool Utrecht from 1995 till 1998. In 1998, she started her study in Human Movement Sciences at the Vrije University in Amsterdam. During this master study, she worked part-time as an exercise therapist in several health care centers, where she provided both individual therapy and sports classes. She graduated in 2001 with a major in Human Movement Sciences and Health Care.

In 2002, Jannique started her scientific career at the Dutch Institute of Allied Health Care (Nederlands Paramedisch Instituut) in Amersfoort, where she worked as a medical librarian and as a research fellow. Later that year, she started her PhD-project at the EMGO-institute, Department of Public and Occupational Health, Vrije University Medical Center in Amsterdam. From autumn 2002 till spring 2007, she conducted the study as described in this thesis. During this period, she also completed the Postgraduate Epidemiology Programme at the EMGO-institute.

As from July 2007, Jannique will continue researching physical activity and population health as a research-fellow at the School of Human Movement Studies, Faculty of Health Sciences, University of Queensland in Brisbane, Australia.

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De stem van de Uffel

Een sparappelvink en een spitskoolmuis
die gingen eens samen op pad;
zei de spitskoolmuis tot de sparappelvink
na een tijdje:' Zeg, hoor je niet wat?'

'Ja, nu je het zegt,' kreet de sparappelvink.
'O, spitskoolmuis, kom, dat 'k je knuffel.
Dat lijkt wel de stem, dat lijkt wel de stem,
dat lijkt wel de stem van de Uffel!'

En de sparappelvink en de spitskoolmuis
huppelden jubelend voort,
want ze hadden de stem, die wondere stem,
de stem van de Uffel gehoord.

Uit: Nieuwe Gorgelrijmen, C. Buddingh', 1985