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 (25th; 75th percentile) was 63 (2; 81) percent of the sessions, and median compliance with taking pills (25th; 75th 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.