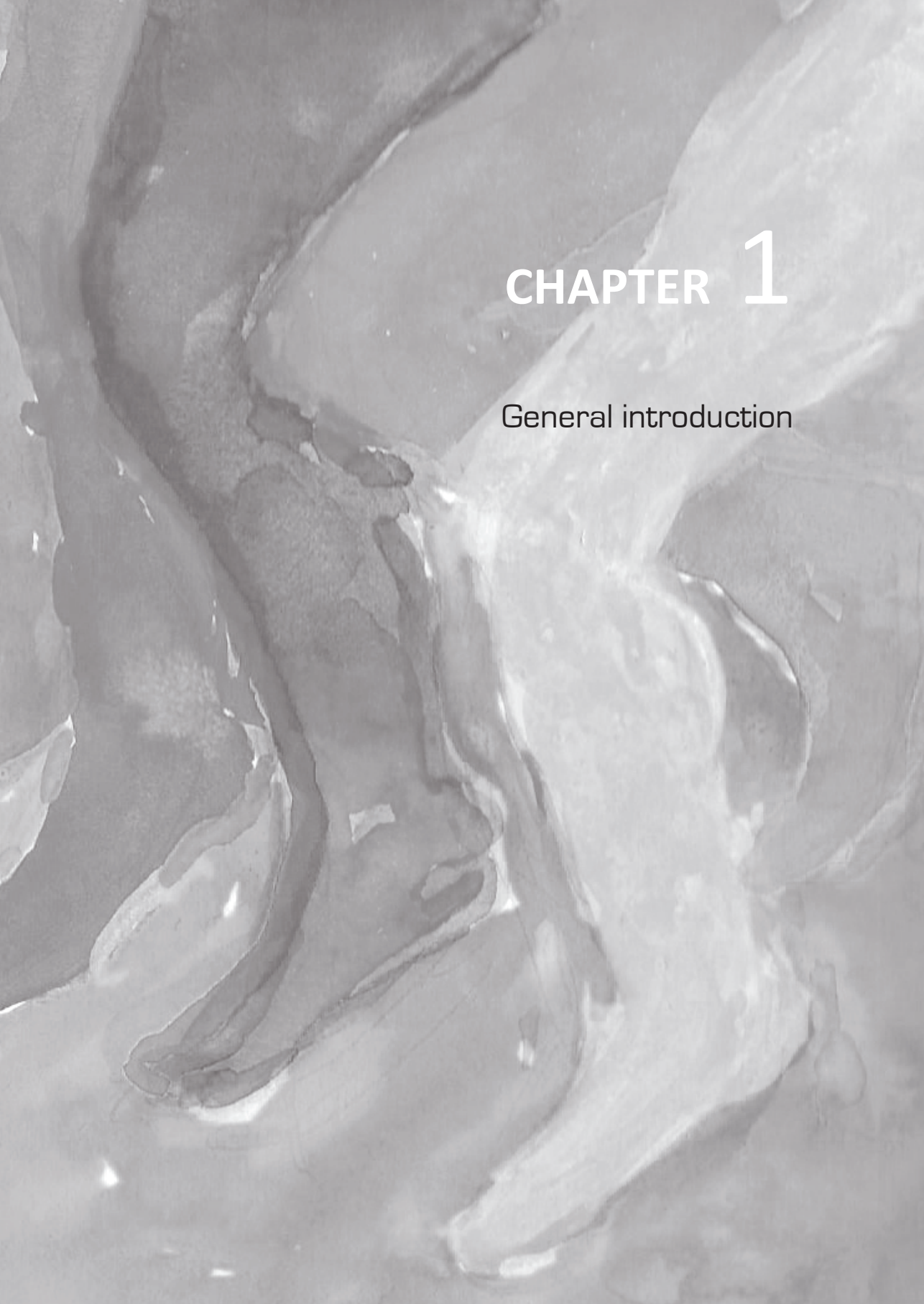

CHAPTER 1

General introduction

Introduction

In this General introduction chapter the background of this thesis is described. First, the problem of osteoporosis will be defined, and the role of homocysteine and B-vitamins will be described, which will result in the objectives of this thesis. Thereafter, the epidemiologic studies that were used in this thesis are shortly introduced, and the outline of this thesis is provided.

Osteoporosis in the aging society

The number and proportion of elderly people is sharply increasing worldwide, and will continue to increase in the nearby future. In The Netherlands, the number of persons aged 65 years or older is expected to increase from 2.6 million in 2011 (16%) to 4.6 million in 2040 (26%).[1] This is a result of an increased life expectancy, and a decrease in birth rate. Although life expectancy has been increasing, those extra years of life are most often not disease-free.[2] The proportion of elderly diagnosed with more than one chronic disease has risen.[1] Also the number of chronic diseases per individual has been increasing.[3] Of the 55-64 years olds, 29% had two or more chronic diseases in 1992, whereas in 2002 41% had two or more chronic diseases.

Osteoporosis is a serious age-related health problem. It is characterized by low bone mass and micro-architectural deterioration of bone tissue.[4] Its major consequence is fractures, which may lead to pain, decline in physical and social functioning, and loss of quality of life.[5] Furthermore, osteoporotic fractures are associated with increased morbidity and mortality.[6] Approximately one in three women will experience an osteoporotic fracture after the age of 50, as will one in five men.[7-9] The economic implications of fractures are substantial: In Europe in 2000, the total direct costs were estimated at €31.7 billion.[10] Because the number of fractures is expected to increase the coming decades, the economic costs associated with fractures will increase accordingly; they are estimated at €76.7 billion in 2050.[10] The increasing prevalence and high costs make the prevention of fractures of major importance.

Homocysteine in older adults

Based on findings from several epidemiologic studies, the circulating homocysteine level has been suggested as modifiable risk factor for fractures.[11-16] Elevated homocysteine levels are frequently observed in the older population, that is, almost 50% of the persons above age 60 has an elevated homocysteine level.[17] Homocysteine increases with age,[17] and is determined by a complex interaction of multiple factors.[18] Deficiencies of vitamin B6, B12,

and folic acid cause a rise in homocysteine levels, as does a common genetic polymorphism, which reduces the enzymatic activity of 5,10-methylene-tetrahydrofolate reductase (MTHFR).[19] Those vitamins and enzyme are involved in the homocysteine metabolism.

Homocysteine is a sulphur-containing amino acid and is part of the methionine metabolism (Figure 1). Methionine is converted to homocysteine, with S-Adenosyl methionine and S-adenosyl homocysteine as intermediates, thereby transferring a methyl group. Methionine is an important source of methyl groups in the synthesis of creatine, methylation of DNA, phospholipids, neurotransmitters, and many other compounds. Homocysteine, in turn, can be either degraded to cysteine via transsulfuration in which vitamin B6 is essential, or remethylated to methionine. In the remethylation pathway, homocysteine is metabolized by methionine synthase in most tissues. Vitamin B12 and the enzyme MTHFR are essential cofactors in this process. Folic acid is needed for the formation of MTHFR. In the liver and kidneys, homocysteine is also remethylated to methionine by betaine-homocysteine methyl transferase.[20]

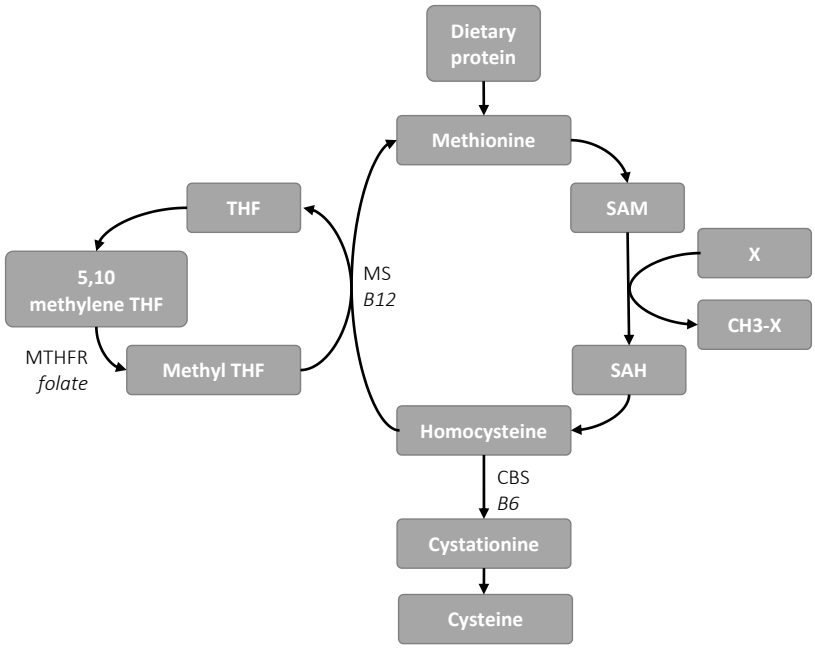

Figure 1 The homocysteine cycle.
CBS= Cystathionine β- Synthase, MS= Methionine Synthase, MTHFR= Methyl Tetrahydrofolate Reductase, SAH= S-Adenosyl Homocysteine, SAM= S-Adenosyl Methionine, THF= tetrahydrofolate.

Nutritional sources of vitamin B12 are animal products, such as meat, fish, eggs, liver, shellfish and dairy products. Folate is present in green leafy vegetables, fruits, meat and dairy products. Among older persons, the prevalence of vitamin B12 deficiency is 6%, and another 20% has a marginal status of vitamin B12.[21] The percentage folate insufficiency in older persons ranges from 2% to 23%. Institutionalized or frail elderly are at highest risk for insufficient concentrations.[22-25]

Vitamin B12 malabsorption from regular foods is the most common cause of low vitamin B12 concentrations, but most elderly can absorb the vitamin from fortified food, or supplementation.[26] The primary cause of low folate concentrations is low intake of folic acid.[26] B-vitamin supplementation can effectively reduce elevated homocysteine concentrations.[27,28] A homocysteine reduction of 20-25% can be achieved by folic acid supplementation, and an additional 7% by vitamin B12 supplementation.[27]

Homocysteine and bone

Several cohort studies showed an increased fracture risk among elderly with mildly elevated homocysteine levels.[11-16] A recent meta-analysis among adults and elderly people reported an increased fracture risk of 4% per µmol/L increase in homocysteine concentration.[29] Although the included studies had a longitudinal design, with the risk factor preceding the outcome, and the results were consistent across studies, definite conclusion with respect to causality of the relation between high homocysteine and an increased fracture risk cannot be drawn from observational data. The question remains whether the increase in fracture risk was due to homocysteine itself, or to other covarying factors, such as general nutritional status. Therefore, homocysteine as an independent risk factor for fractures needs to be confirmed in randomized controlled trials. If homocysteine emerges to be a causal factor for fractures, homocysteine lowering might become a target in the prevention of fractures with major public health implications.

Another criterion for the determination of causality in epidemiology is a biological plausible mechanism at work.[30] Several mechanisms are suggested by which homocysteine might affect bone strength. The mechanism may involve a homocysteine-induced change in collagen cross-linking. This hypothesis is derived from clinical observations among patients with homocystinuria, which is an autosomal recessive disease that causes high levels of homocysteine, atherosclerosis, and osteoporosis. Among those patients, disturbed bone collagen profiles are observed with subsequent fragile bones.[31-33] Moreover, evidence suggests that high homocysteine and low vitamin B12 concentrations activate osteoclast (bone resorbing cell) formation and activity.[34,35] An alternative explanation might be found in reduced muscle strength, physical performance, and a subsequent increased risk for falling.

Osteoporotic fractures and physical functioning

The probability for bone to fracture depends on both the strength of the bone and forces applied to the bone. When the external load on the bone exceeds its strength, the bone will fracture.[36] Bone strength is determined by many components, including its mass, material and geometric properties.[37] Mechanical loading by muscular and gravitational forces has positive effects on those properties.[38,39] Especially high-impact loading activities are beneficial in fracture prevention.[39] This direct effect of muscle activity on bone strength emphasizes the importance for older persons to maintain an active lifestyle.

Also indirect effects of physical functioning on fracture risk are known. Physical abilities commonly decline with aging. Persons with a reduced physical functioning are more susceptible to fall,[40] due to muscle weakness and slow neuromuscular reactions.[41] One in three persons older than 65 years falls at least once a year and 15% falls at least twice.[42,43] Falls may induce high loads to the bone. Consequently, 5% of the falls leads to a fracture.[44]

Reductions in muscle strength and physical performance, and falling may be an intermediate pathway by which high homocysteine induces an increased fracture risk in older persons. Homocysteine has been suggested to have effects on multiple systems, including vascular and neuromuscular systems,[e.g.18] and these systems may affect mobility and gait. Therefore, a role for homocysteine as potential modifiable risk factor for decline in physical functioning is suggested. Limited evidence is available for the association between homocysteine and physical functioning in older adults.

Objectives

This thesis aims to contribute to the understanding of the association between high homocysteine and increased fracture risk in older persons. The main objective is to examine the effect of homocysteine-lowering by B-vitamin supplementation on fracture incidence. Second, potential mechanisms at work are considered by examining the association of homocysteine with different aspects of physical functioning and falling, and examining the effects of homocysteine-lowering therapy on physical functioning and falling, and on bone characteristics, including bone mineral density and quantitative ultrasound parameters. Figure 2 systematically depicts potential pathways.

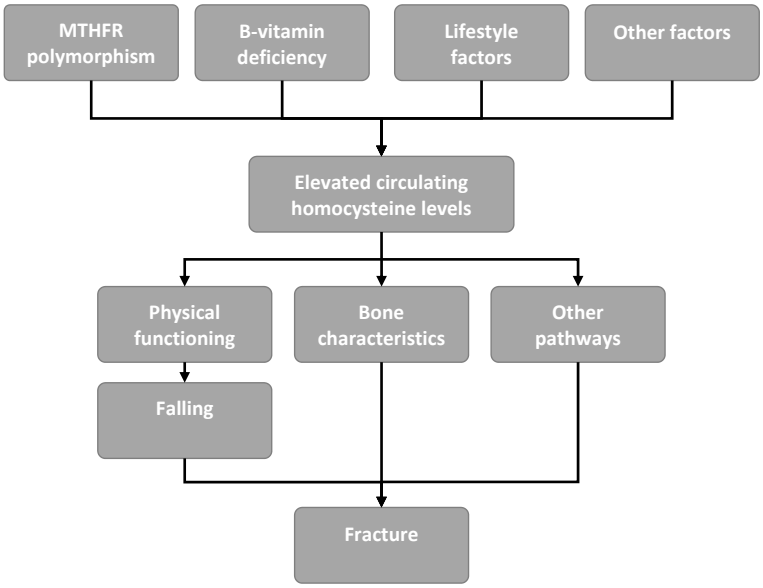

Figure 2 Potential pathways from elevated homocysteine levels to an increased fracture risk.

The epidemiologic studies used in this thesis

This thesis is based on data from the Longitudinal Aging Study Amsterdam (LASA) and the B-vitamins for the PRevention Of Osteoporotic Fractures (B-PROOF) study.

The LASA is an ongoing cohort study in the Netherlands that studies determinants, trajectories and consequences of physical, cognitive, emotional and social functioning in older persons.[45] The LASA started in 1992-1993 with 3,107 respondents initially aged 55-85 years. A nationally representative sample was drawn from population registries of eleven municipalities in the Netherlands. The sample was stratified for age, gender, and 5-year life-expectancy. Older old, especially older men were therefore oversampled. Approximately every 3 years, data were collected in a main face-to-face interview, a medical face-to-face interview, and a self-administered questionnaire.[45]

The main aim of the B-PROOF study was to examine the effect of vitamin B12 and folic acid supplementation on fracture incidence in a general population of older adults.[46] A total of 2,919 persons aged 65 years or older with mildly elevated homocysteine levels (12-50 µmol/L) were included in this randomized controlled trial. Participants who were assigned to the intervention group received a daily tablet with 400 µg folic acid, 500 µg vitamin B12, and 600 IU vitamin D3; the placebo tablet contained 600 IU vitamin D3 only. Falls and fractures were recorded prospectively on a weekly calendar. Blood sampling and a face-to-

face interview were conducted at baseline and follow-up, with emphasis on physical functioning, cognition, cardiovascular outcomes, and quality of life.

Outline of this thesis

The rationale and design of the B-PROOF study are described in more detail in Chapter 2. In the next four chapters, association studies are described. Chapter 3 reports cross-sectional and longitudinal findings on homocysteine and vitamin B12 in relation to physical performance within the LASA. In Chapter 4, other aspects of physical functioning in relation to homocysteine are reported, including muscle mass, muscle strength, physical activity, functional limitations, and falling in the LASA. Next, we studied MTHFR polymorphisms and homocysteine, as well as their interaction in relation to physical performance and muscle function, using baseline data from the B-PROOF study (Chapter 5). In Chapter 6, the association between serum folate and inflammation within the B-PROOF study are described. The following three chapters report effects of vitamin B12 and folic acid supplementation, using follow-up data of the B-PROOF study. Effects on fractures (Chapter 7), physical performance, handgrip strength, and falling (Chapter 8), and bone mineral density, and quantitative ultrasound parameters (Chapter 9) are described. In the general discussion of Chapter 10, the main findings of this thesis are summarized, their interpretation and methodological considerations are reflected on, as well as implications for future research and clinical implications.

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chapter

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