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Multimorbidity challenges physical activity

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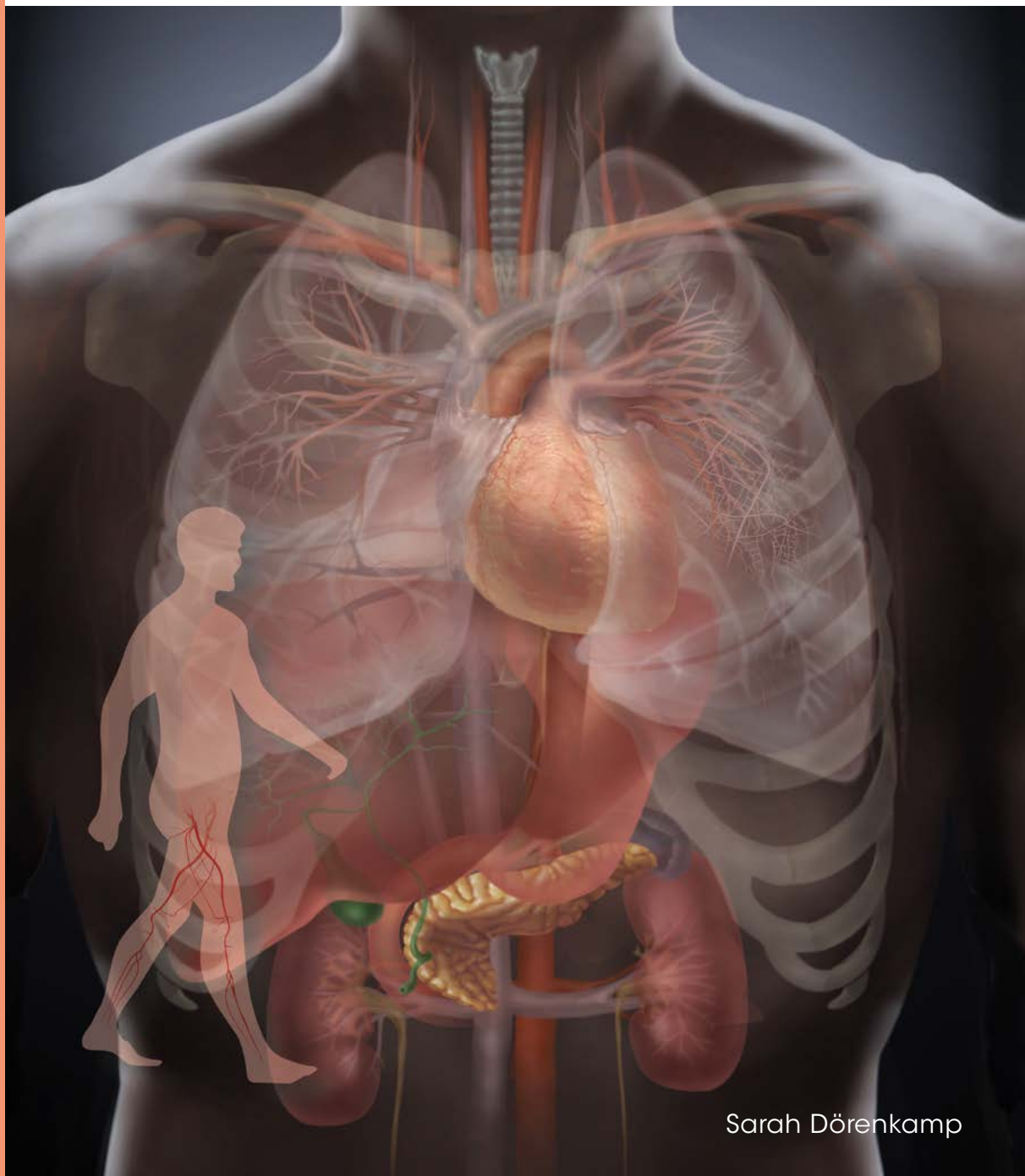
MULTImorbidity challenges Physical Activity

- implications for targeting patient treatment -



Sarah Dörenkamp

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– Implications for targeting patient treatment –

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Für Mama und Papa

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Chapter 1

General introduction

This thesis focuses on multimorbidity, comorbidity and physical activity. Since these concepts are complex and the introductions to the individual chapters can only provide a brief presentation of these topics, the aim of this general introduction is to provide an elaborate explanation of these underlying concepts.

Preface

Due to technological advances and improvements in living conditions, medical care and public health policy, a large number of patients now survive medical conditions that used to be fatal [1-3]. As a result of this phenomenon, combined with increased aging, there is a growing number of patients who have multiple coexisting chronic diseases, also referred to as multimorbidity [4]. The prevalence of multimorbidity is continuously rising, but a lack of consensus on the operational definition of multimorbidity together with a lack of comparability between studies (e.g. design and population selected) makes it impossible to establish a unique prevalence estimate. In the Netherlands, the prevalence of chronic diseases has doubled between 1985 and 2005 [2]. It is estimated that approximately 37% of all patients aged 55 years and older have multimorbidity and that with age this prevalence increases up to 78% in subjects aged 80 years and over [4]. The proportion of patients with one or two chronic diseases remained relatively stable. In contrast, the number of patients with three chronic diseases increased by approximately 60%, while the number of patients with four or more chronic diseases saw a remarkable increase of approximately 300% [2].

The ongoing growth in the number of patients with multiple diseases calls for adequate identification of strategies for optimal treatment, and prevention of further deterioration [5]. With obvious benefits, regular physical activity participation has been shown to prevent and/or treat almost every chronic disease successfully [6]. According to the World Health Organisation, physical activity is defined as any bodily movement that is produced by skeletal muscles that requires energy expenditure [7]. In this thesis we looked at physical activity in three different ways. First, we expressed physical activity in meters walked. Second, we measured physical activity as compliance/ non-compliance with the Dutch physical activity guideline, which states that every adult aged 55 years and over should accumulate 30 minutes or more of moderate intense physical activity (3 to 5 METs) on at least five, or preferably all days of the week [7]. Third, we studied specific physical activity behavior performed (i.e. walking, cycling, gardening, odd jobs, light and intense household activities and sports).

TERMINOLOGY

Several definitions of multimorbidity can be found, and consensus on the terminology to describe the coexistence of diseases is still lacking [8]. In this dissertation the definitions from Boyd and Fortin [1] will be used as point of departure.

Multimorbidity refers to any co-occurrence of two or more chronic medical or psychiatric conditions in the same individual, which may or may not interact with each other and where one condition is not necessarily more central or important than the other (Figure 1) [1, 2, 9, 10].

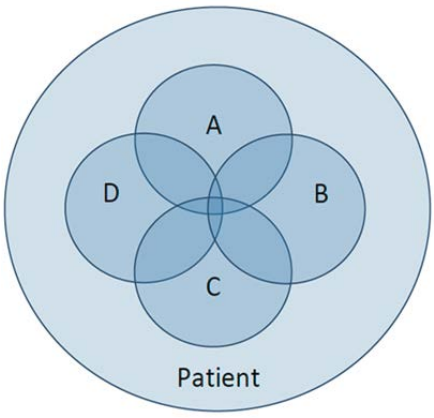


Figure 1. Conceptual diagram of multimorbidity. Four co-occurring conditions within the same individual that may or may not interact with each other (Adapted from Boyd and Fortin [1]).

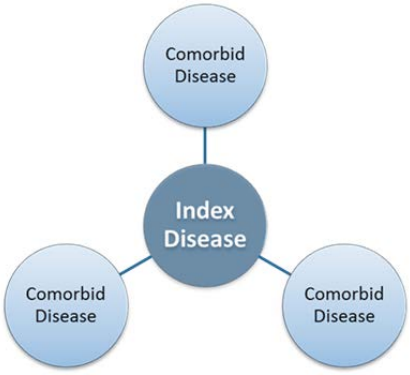


Figure 2. Conceptual diagram of comorbidity. Index disease with three comorbid conditions that may or may not affect the course or treatment of the index disease (Adapted from Boyd and Fortin [1]).

The term comorbidity is often used interchangeably with multimorbidity. Comorbidity has often been treated in clinical practice from the perspective of an index disease which has a central place. Coexisting diseases may affect the course and/or treatment of this index disease (Figure 2) [11, 12]. This scenario implies the need for prioritization, i.e., establishing which disease is most important for the patient in terms of care and well-being [13]. The first part of this thesis concentrates on coexisting diseases and their impact on treatment outcome, defined here in terms of physical activity performed as part of standard physiotherapy care. Peripheral arterial disease is used as the index disease to illustrate the concept of comorbidity. The following paragraphs will give a short description of peripheral arterial disease, risk factors and its management.

PERIPHERAL ARTERIAL DISEASE

Peripheral arterial disease is an atherosclerotic disease in which the arterial lumen is progressively narrowed by atherosclerotic plaques. An atherosclerotic plaque develops in the intima of the vascular wall and is composed of an accumulation of lipids, inflammatory cells and smooth muscle cells [14]. This atherosclerotic plaque may partially or completely block the blood flow through an artery (Figure 3).

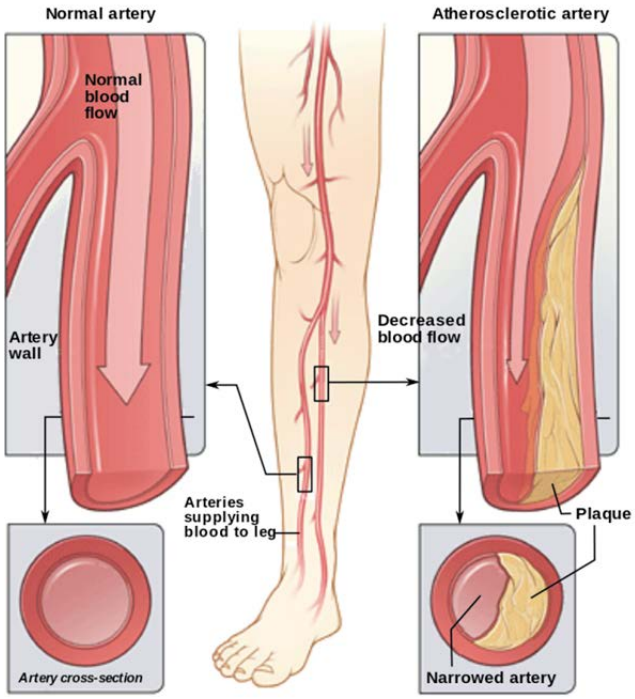


Figure 3. A comparison of a normal artery and an artery with an atherosclerotic plaque. Figure A illustrates a normal artery and Figure B shows an artery with a plaque that partially reduces the blood flow. The inset image shows a cross-section of a normal artery and an artery with an atherosclerotic plaque (Source: National Heart, Lung, and Blood Institute; National Institutes of Health; U.S. Department of Health and Human Services; permission obtained).

Peripheral arterial disease affects approximately 15% of the adult population aged over 69 years [15]. It is estimated that approximately 20 million people in Europe and 202 million people worldwide suffer from peripheral arterial disease [16]. The symptoms of peripheral arterial disease are classified by Rutherford and Fontaine. Rutherford stages 1-3 describe mild, moderate and severe intermittent claudication, respectively. When pain is also experience at rest or during the night stage 4 has been reached and ulcera-

tion or necrosis denotes stage 5 and 6. Fontaine stage IIa and IIb are comparable with stage 1 and 2 of Rutherford. Maximum walking distance ≥ 100 meters is described as Fontaine IIa and maximum walking distance < 100 meters as stage IIb. Fontaine stage III denotes pain at rest and stage IV ulceration or necrosis [17].

Intermittent Claudication, most notably cramping, pain or tiredness in the leg during walking or climbing stairs, is the main symptom of peripheral arterial disease. Approximately 30% to 40% of patients with peripheral arterial disease experience claudication symptoms. These symptoms are prominent in one leg and relieved by rest [18]. Patients with intermittent claudication do not experience pain while standing, seating or resting, because then the blood flow is sufficient. However, during times of increased metabolic demand, such as during walking and physical activity, the restricted blood flow to the leg muscles results in a mismatch of oxygen supply and metabolic demand which causes intermittent claudication [19].

When associated with intermittent claudication, atherosclerotic peripheral arterial disease results in a moderate to severe impairment in walking ability [20]. Consequently, patients suffering from intermittent claudication are hampered in their ability to exercise and to carry out normal daily activities. This negatively affects their health risk profile for other chronic diseases.

MORBIDITY AND MORTALITY ASSOCIATED WITH PERIPHERAL ARTERIAL DISEASE

Morbidity and mortality risks from associated coronary artery disease and cerebrovascular disease are increased in peripheral arterial disease patients [15]. Overall, the prevalence of coronary artery disease and cerebrovascular disease in patients with peripheral arterial disease is 40% to 60% and 26% to 50%, respectively [15]. Patients with intermittent claudication are five times more likely to suffer from a cardiac event and more than twice as likely to get a major adverse cardiac event compared to peripheral arterial disease patients without intermittent claudication [21]. The mortality rate of patients with peripheral arterial disease is comparable to that of non-peripheral arterial disease patients who are 10 years older. Compared to age-matched healthy persons, the mortality rate of patients with peripheral arterial disease is significantly higher at approximately 12% per year [22]. All-cause mortality rates for patients with peripheral arterial disease are 30% after 5 years of diagnosis, 50% after 10 years of diagnosis and 70% after 15 years of diagnosis [15].

RISK FACTORS FOR PERIPHERAL ARTERIAL DISEASE

The etiological risk factors for the development of peripheral arterial disease are comparable to patients at risk for atherosclerosis and cardiovascular disease. Among others, risk factors which can be influenced include inadequate physical activity behavior, smoking, hypertension, hyperlipidemia and diabetes mellitus [22, 23]. Sex and age are risk factors that cannot be altered.

Inadequate physical activity behavior

Previous research has shown that inadequate physical activity behavior, defined as non-compliance with physical activity guideline recommendations, has a negative impact on vascular biomarkers in peripheral arterial disease. Insufficient physical activity is associated with a greater expression of inflammatory markers, coagulation, lipid profiles, glucose, endogenous fibrinolysis and insulin resistance [24-26]. It seems that inadequate physical activity through fewer muscle contractions alters myokine response in the skeletal muscle causing an increased proinflammatory status [27]. Regarding the association between physical activity guideline non-compliance and cardio-metabolic biomarkers, a review suggested that insufficient muscle contractions suppress lipoprotein lipase activity, reduce triglyceride uptake and HDL levels and increase insulin resistance. Moreover, insufficient physical activity seems to impair endothelial function through arterial wall stiffening and narrowed artery diameter [28]. Together, these factors lead to a poorer health prognosis in patients with peripheral arterial disease.

Smoking

Smoking is a key risk factor for the development and progression of peripheral arterial disease, and studies show evidence of a dose-dependent effect [29-31]. The risk of peripheral arterial disease seems to be four times higher in smokers compared to non-smokers [32], and smoking has been reported to be associated with 78% of the patients with intermittent claudication [33]. Smokers are at increased risk for peripheral arterial disease, as smoking damages the endothelium and thereby makes arteries prone to atherosclerosis [34]. A study by Ingolfsson et al. [29] demonstrated that smoking cessation is associated with a decline in the incidence of peripheral arterial disease and that the risk of developing peripheral arterial disease is already comparable between non-smokers and ex-smokers one year after quitting. The risk of cardiovascular disease diminishes within two to four years after smoking cessation. Therefore, smoking cessation is deemed one of the most preventable causes of peripheral arterial disease [34, 35].

Hypertension

Hypertension is defined as a systolic blood pressure ≥ 140 mmHg and/or a diastolic blood pressure ≥ 90 mmHg. Hypertension puts extra strain on the arteries and may damage them [36, 37]. As a result, fatty deposits (atherosclerosis) can build up around the damaged areas, leading to narrowed arteries and in turn resulting in poor circulation [38]. Hypertension increases the risk of developing peripheral arterial disease two- to threefold [39].

Hyperlipidemia

The prevalence rate of hyperlipidemia is 77% in patients with peripheral arterial disease [40]. Cholesterol travels through the bloodstream in two types of lipoproteins: (1) low-density lipoproteins and (2) high-density lipoproteins. If too much low-density lipoprotein cholesterol circulates in the blood, it decreases nitric oxide bioavailability, which causes low-density lipoproteins to enter into the arterial intima and to build up together with other substances in the inner walls of the arteries (plaque formation) [41]. In contrast, high-density lipoprotein cholesterol counteracts atherosclerosis. It removes cholesterol from foam cells, inhibits the oxidation of low-density lipoprotein, restricts inflammation and carries cholesterol back to the liver, where it is then removed from the body [40, 41].

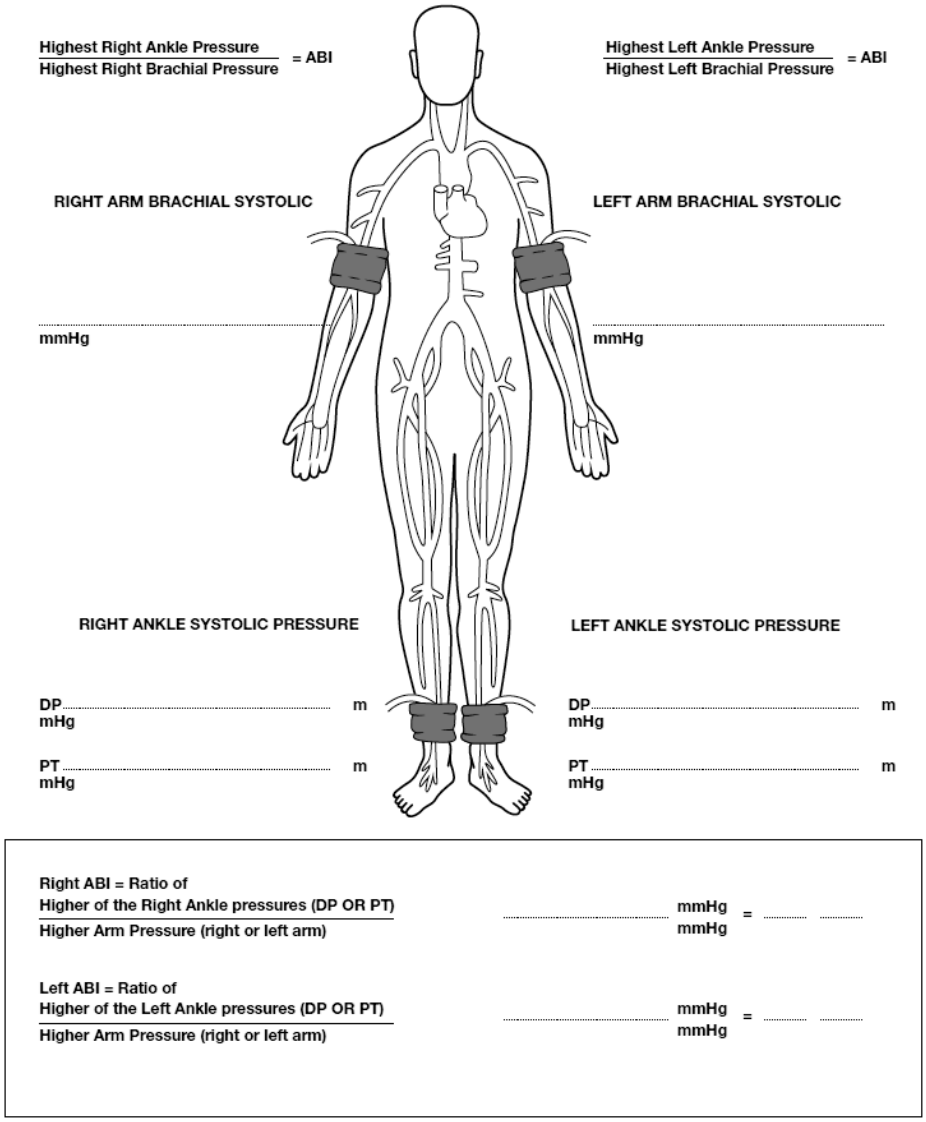
Diabetes Mellitus

Insulin is needed to transport glucose from the blood into the cells where it can be used to produce energy. Diabetes means the body is unable to produce insulin or to use insulin efficiently, resulting in hyperglycemia, free fatty acids and oxidative stress which damages arteries and induces vasoconstriction, inflammation and thrombosis via hypercoagulation [42, 43]. A two- to fourfold increase in the chance to develop peripheral arterial disease has been found in patients with diabetes mellitus [44]. Moreover, lower extremity function has been reported to be worse in patients with peripheral arterial disease and diabetes compared to patients with peripheral arterial disease only [44]. The role of diabetes mellitus in peripheral arterial disease seems to be related to increased glycosylated hemoglobin (HbA1c). A study by Selvin et al. [45] showed a positive independent association between HbA1c levels and peripheral arterial disease risk in patients with diabetes.

DIAGNOSIS OF PERIPHERAL ARTERIAL DISEASE

The Ankle-brachial index (ABI) is a reliable and valid method to diagnose peripheral arterial disease. To determine the Ankle-brachial index, the patient has to be in the supine position for at least 10 minutes. First the systolic blood pressure (the force that blood exerts on the artery walls when the heart contracts to pump out blood) of both brachial arteries is measured. Second, blood pressure cuffs are put proximal to the malleoli on each leg. A Doppler ultrasound blood flow detector probe is then placed over the arteries (dorsalis pedis artery and posterior tibial artery) in the lower leg. To calculate the Ankle-brachial index, the highest systolic blood pressure of each leg is divided by the highest systolic blood pressure of both arms. In healthy individuals pulse wave reflection causes the ankle pressure to be 10 mmHg to 15 mmHg higher, resulting in a normal Ankle-brachial index ratio of 1.00 or just greater than 1.00. In general, an Ankle-brachial index between 0.9 and 1.2 is considered normal, while an ABI < 0.9 indicates arterial disease [46, 47]. An Ankle-brachial index value > 1.2 suggests noncompressible arteries and calcification of the artery walls (Figure 4) [48].

The Ankle-brachial index also serves as marker for overall atherosclerotic burden, as an Ankle-brachial index < 0.9 is associated with a higher all-cause mortality rate, a greater cardiovascular disease burden and the presence of atherosclerotic risk factors [44, 49].



*ABI = Ankle Brachial Index; DP = Dorsalis Pedis; PT = Posterior tibial

Figure 4. A protocol to measure the Ankle-brachial index (ABI).

MANAGEMENT OF PERIPHERAL ARTERIAL DISEASE

There are different treatment options for patients with peripheral arterial disease. Treatment includes cardiovascular risk management involving lifestyle modification and

symptomatic therapy. Antiplatelet and statin therapy are part of the cardiovascular risk management to treat hypertension and diabetes. Lifestyle modification involves increasing physical activity, smoking cessation and weight reduction. Surgical or endovascular revascularization, are often only mentioned as secondary treatment options. The first-line treatment for intermittent claudication is supervised exercise therapy.

Surgical or endovascular revascularization

Patients with rest pain, intermittent claudication or limb-threatening ischemia are suited for revascularization. Revascularization can be achieved through leg bypass surgery or percutaneous balloon angioplasty with or without stenting.

Leg bypass surgery involves the insertion of a tube (graft) that acts as a new vessel. This graft can be a vein taken from a different location of the patient's leg, contralateral leg or even the arms or can be made from synthetic material. The 'new' vein reroutes the blood flow around the blocked artery (Figure 5). Percutaneous transluminal angioplasty (PTA) is a method of mechanically widening the narrowed or obstructed artery. A small empty and collapsed balloon is introduced with a catheter into the narrowed part of the artery. When the balloon is inflated to a set size, it stretches and opens the artery and thereby improves blood flow. Afterwards the balloon is deflated and withdrawn. Based on certain criteria a 'stent' (metallic tubular) can be inserted [47] (Figure 6).

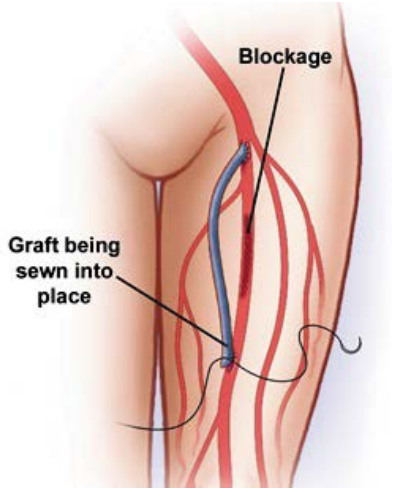


Figure 5. Femoropopliteal Bypass Surgery (Source: http://www.indiahospitaltour.com/heart/peripheral-vascular-surgery-india.html; permission obtained).

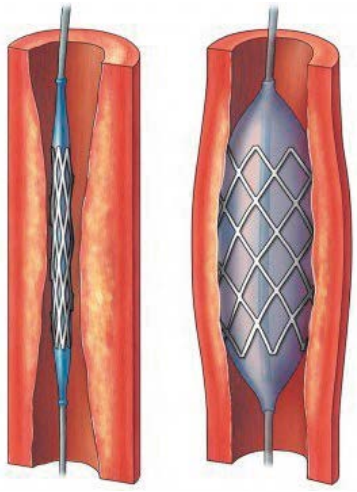


Figure 6. Balloon/stent positioned and expanded (Source: http://www.indiahospitaltour.com/heart/peripheral-vascular-surgery-india.html; permission obtained).

Supervised exercise therapy

The majority of patients suffering from mild to moderate intermittent claudication are referred to the physiotherapist for exercise therapy in combination with a modification of cardiovascular risk factors. A meta-analysis published by Gardner et al. [50] demonstrated that supervised exercise training has a positive effect on claudication symptoms and increases maximum pain-free walking distance by more than 100%. Another systematic Cochrane review also showed that physiotherapy markedly improves walking ability in patients with peripheral arterial disease, and improvements in claudication symptoms lasted in the supervised exercise training group up to two years [51]. In addition, exercise training has beneficial effects on cardiovascular risk factors by improving blood pressure, serum lipid profile and glycemic control.

In the Netherlands, recommendations on the content and duration of supervised exercise training are described in the evidence-based guideline symptomatic Peripheral Arterial Disease of the Royal Dutch Society for Physiotherapy. The guideline recommends supervised walking exercises on a treadmill at least three times a week for at least 30 minutes per exercise session for a minimum of 6 months [52]. Exercise intervals should last for at least 3-4 minutes with (almost) complete recovery during the rest period. Patients should walk at a speed and incline that elicits claudication symptoms, and then continue to walk until they reach symptoms of intense claudication [52]. The claudication pain rating scale of the American College of Sports Medicine (ACSM-scale) [53] is often used during training to assess the level of pain. Disease severity, functional impairment and supervised exercise treatment progress in patients with intermittent claudication is usually quantified by the measurement of Initial Claudication Distance (ICD, also referred to as maximum pain-free walking distance), the distance at which the patient experiences the onset of claudication pain and the Absolute Claudication Distance (ACD, also termed maximum walking distance), the distance at which the pain forces the patient to stop walking. A cut-off for initial claudication distance is set at 1600m, because incline and testing duration in standard practice are maximized to 30 minutes. In this thesis we use initial claudication distance as outcome measure since we want to acknowledge the patient's perspective. However, in our systematic review (chapter 5) we use absolute claudication distance as outcome measure. We did so because most studies conducted on the effects of supervised exercise therapy in patients with intermittent claudication focus on absolute claudication distance only and we want to be able to include those into our systematic review.

POSSIBLE MECHANISMS FOR THE EFFECTS OF SUPERVISED EXERCISE THERAPY

Supervised exercise therapy has been recommended as first-line therapy for the treatment of patients with peripheral arterial disease due to its potential to improve functional capacity, to interrupt functional decline and to reduce cardiovascular events [54]. Nevertheless, there is still a debate about the mechanisms responsible for improvement and the underlying peripheral physiological adaptations that occur due to supervised exercise training. Evidence supports the role of endothelial dysfunction, mitochondrial dysfunction, arterial obstruction and inflammatory activation (Table 1).

Endothelial dysfunction

The endothelium is a monolayer of cells between the lumen and the smooth muscle cells in arteries. In endothelial cells, amino-acid L-arginine synthesizes vasoprotective Nitric Oxide (NO) through the enzyme Nitric Oxide Synthase (NOS) to regulate arterial blood flow [55]. Nitric oxide maintains vascular homeostasis through modulation of the vascular dilator tone, regulation of cell growth and vessel protection against circulating platelets and cells in the blood. It mediates its vasodilator effect by activating guanylate cyclase, an enzyme which is necessary for the production of cyclic guanosine monophosphate (cGMP), a major initiator of vascular relaxation [56]. The risk factors for atherosclerosis associated with peripheral arterial disease, like hypertension, smoking, hypercholesterolemia and diabetes mellitus seem to be associated with a decreased release of nitric oxide either due to impaired synthesis or oxidative degradation. Moreover, consistent with the loss of nitric oxide activity an impaired endothelial vasodilator response has been detected in patients with peripheral arterial disease [57, 58].

Several studies have investigated the ability of exercise to reverse endothelial dysfunction by increasing nitric oxide release from the endothelium [59]. Two studies found an improvement in endothelial function after supervised exercise therapy in patients with peripheral arterial disease. In a study by Brendle et al. [60], supervised exercise therapy increased endothelium-dependent dilation of the brachial artery by 65%. McDermott et al. [61] also detected enlarged flow-mediated dilation after treadmill exercise consistent with improvements in endothelial health. The underlying physiological mechanisms may be related to an increase in shear stress that stimulates nitric oxide expression and activation [62, 63].

Mitochondrial dysfunction

Vascular obstruction adversely affects the distal skeletal muscle phenotype in peripheral arterial disease patients. Imaging studies show a reduced overall area, a decreased muscle density and increased fat content [64-66]. Furthermore, evidence exists for increased muscle apoptosis, a decreased level of type I fibers and a reduced capillary density in patients suffering from peripheral arterial disease [67, 68]. These altered cellular and structural changes cause intermediate metabolites of substrate oxidation to accumulate in the blood and the muscle, leading to impaired mitochondrial function. As a consequence, the divergent mitochondrial function obstructs energy production and stimulates the generation of reactive oxygen species (ROS) [69-71], which in turn disrupt skeletal muscle oxygen utilization and induce endothelial damage [72, 73].

Mitochondrial function and skeletal muscle metabolism seem to be positively influenced by regular exercise training. Increased physical activity is related to improved mitochondrial energetics via peroxisome proliferator-activated receptor-gamma coactivator 1α (PGC-1α), a regulator of mitochondrial biogenesis and favorable muscle traits. Proliferator-activated receptor-gamma coactivator 1α seems to be a key regulator of mitochondrial biogenesis, and the expression of PGC-1α is therefore often used as marker of this process. Interval and concurrent exercise training seems to upregulate PGC-1α, thereby improving mitochondrial function and skeletal muscle metabolism [74].

Arterial obstruction

In patients with peripheral arterial disease, atherosclerosis diminishes blood flow to the muscles of the leg(s). Animal studies have shown that exercise enhances peripheral arterial blood supply [75-77]. Growth factor activity and increased nitric oxide concentration lead to angiogenesis, as a result of which peripheral blood supply increases [78]. However, studies including patients with peripheral arterial disease were not able to replicate these findings detected in animal models. Some exercise training studies [79-81] show an increase in blood flow, but these findings were not consistent [82]. One factor that might explain the observed difference in findings between animal and human studies is the concomitant endothelial dysfunction in peripheral arterial disease patients that might impede sufficient collateral growth [83].

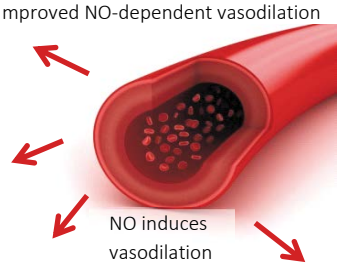
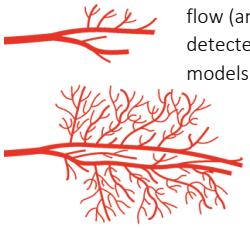
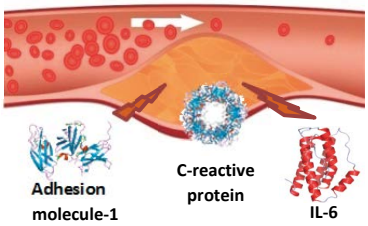
Inflammatory activation

Inflammatory markers like C-reactive protein (CRP), interleukin-6 (IL-6) and vascular cell adhesion molecule-1 (VCAM-1) play a role in atherosclerosis [84-88]. They favor plaque

growth, induce skeletal muscle injury, inhibit nitric oxide production and impede vasodilation [86]. A study by McDermott et al. [87] shows a direct association between C-reactive protein, interleukin-6, vascular cell adhesion molecule-1 and decreased calf muscle area and increased calf muscle fat content.

Epidemiological data shows a decreased level of inflammatory markers in people performing regular physical activity compared to those with a sedentary lifestyle [88]. To be more precise, a study by Craft et al. [89] detected an inverse association between physical activity and C-reactive protein, interleukin-6 and vascular cell adhesion molecule-1. A number of other cross-sectional studies presented an association between physical activity and lower plasma concentrations of interleukin-6, tumor necrosis factor alpha (TNFα) and C-reactive protein in various age groups, including the elderly [90-92]. In summary, physical activity not only improves physical function and helps people remain independent, but also seems to attenuate systemic inflammation.

Table 1. Physiological and biological mechanisms of Peripheral Arterial Disease and the effects of exercise training.

Physiological mechanism	Functional consequence	Effect of exercise training
Endothelial dysfunction ↓ release of Nitric Oxid (NO)	↑ Platelet and leukocyte adhesion and aggregation (formation of plaque) ↑ Oxidation of LDL cholesterol (major component of plaque) ↑ Stimulation of transcription factor activity NF-κB and expression of adhesion molecules ↑ Expression of inflammatory mediators (MCP-1, Il-6, IL-8, MCSF) ↓ Decreased elasticity ↓ Vasodilation (decreased blood flow)	▪ Improved coronary endothelial function ▪ Improved NO-dependent vasodilation 
Mitochondrial dysfunction ↓ obstructed energy production	↓ Overall muscle area ↓ Muscle density ↑ Fat content ↑ Muscle apoptosis ↓ Type I fibers ↓ Capillary density ↑ Accumulation of metabolites of substrate oxidation in blood and muscle ↑ Generation of reactive oxygen species (ROS)	▪ Improved mitochondrial energetics ▪ Leads to favorable muscle traits Enhanced metabolic function and performance
Arterial Obstruction	↓ Impaired peripheral blood flow	 Increase in collateral flow (angiogenesis) detected in animal models
Inflammatory activation ↑ atherosclerotic progression	↑ Favoring plaque growth ↑ Inducing skeletal muscle injury ↓ Impede vasodilator function ↓ Lower calf muscle area ↑ Higher calf muscle fat	▪ Decreased level of inflammatory markers 

In elderly patients, comorbidity often complicates treatment, for example when supervised exercise therapy for peripheral arterial disease interacts negatively with or even

counteracts the treatment of another coexisting chronic disease. Currently, physiotherapists have limited guidance or evidence as to how to make treatment decisions in patients suffering from comorbidity. As a consequence, patients with comorbid conditions often receive care that may be inefficient and ineffective [93-96]. The following paragraphs discuss the principles of evidence-based medicine, in order to help understand the challenges of limited guidance and restricted evidence about best practice in physiotherapy care for patients with peripheral arterial disease and comorbidity.

EVIDENCE-BASED MEDICINE, CLINICAL GUIDELINES AND MULTIMORBIDITY

Evidence-based medicine (EBM) is defined as the "conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients" [97]. This implies that in evidence-based clinical practice the best available evidence is used, in consultation with the patient, to decide upon the treatment option which suits that individual patient best. In order to inform the physician about the best available evidence, Clinical Practice Guidelines (CPGs) are commonly used. The Institute of Medicine (IOM) defines clinical practice guidelines as "statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options" [98]. To date, however, research, pharmacological treatments and practice guidelines have focused on the management of isolated chronic conditions [99-101]. With rare exceptions, guidelines take little account of comorbidity as experienced by most patients [102]. In a review, Boyd and colleagues [95] investigated the existence of components relevant to the care of older patients with comorbidity in nine common chronic conditions and selected primary and specialty care practice guidelines that were recommended by national or international organizations. It was shown that only a few practice guidelines address issues related to comorbidity, and that none of the guidelines comprehensively focused on this issue. The applicability of clinical practice guidelines is therefore modest for patients with comorbidity [99].

The root of this problem lies in the translational path from evidence generation to evidence synthesis. Selective eligibility criteria of randomized controlled trials are considered crucial to the feasibility and internal validity of trials. Enrolling participants with similar characteristics helps researchers achieve accurate and meaningful results by ensuring that the result occurred due to the factor being studied and not due to co-factors [103]. However, the exclusion of certain patient populations and/or the inability of such populations, like older adults with comorbidity, to participate in these random-

ized controlled trials may hamper the generalizability of results. After all, the population included in clinical trials should adequately represent the whole population treated in clinical practice [103].

Regardless of whether there is a homogeneous treatment effect in randomized controlled trials with a selective study sample, the treatment effect could still be heterogeneous in the daily practice population. Figure 4, adapted from Kravitz et al. [104], shows the discrepancy between homogeneity of patients enrolled in randomized controlled trials and heterogeneity in the daily practice population. First, a carefully selected homogeneous study sample used in randomized controlled trials might underestimate the heterogeneity of the treatment effect in the target population (Sample 1 in Figure 7). In patients that satisfy the narrowly defined eligibility criteria of randomized controlled trials the treatment might have a uniform effect; however, this effect may not be homogenous in the daily practice population. Second, if the treatment under study has a diverging effect on the patients included in randomized controlled trials, the average effect of the treatment might be under- or overestimated (Sample 2 in Figure 7) in the daily practice population, partly composed of patients that do not satisfy the eligibility criteria of randomized controlled trials. Sample 3 shows what a representative sample of the daily practice population would look like.

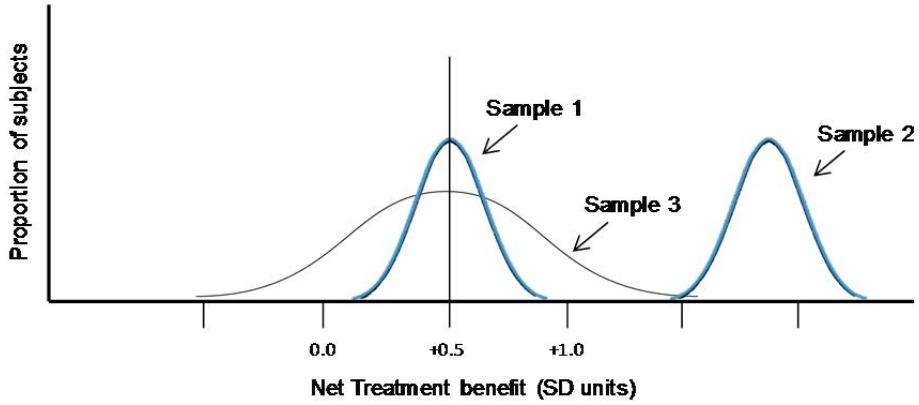


Figure 7. Distribution of the individual treatment effect in three hypothetical study samples (modified from Kravits et al. [104]).

This can have a number of important implications. For instance, if the average effect as reported in randomized controlled trials does not apply to the majority of the target population, health care providers could end up over- or undertreating patients. Moreover, it could result in erroneous recommendations in daily practice, in case clinical guidelines inadvertently encourage health care providers to discount differences between

their own patients and those studied in the primary trials. In short, health care providers have little guidance as to how to care for patients with multimorbidity because current clinical practice guidelines are mostly focused on eligible patients, who often have one disease at the time. Therefore, information on highly prevalent combinations of diseases, their underlying relationship and associated consequences assessed in a primary care population may support guideline development in case of multimorbidity.

MULTIMORBIDITY AND THE MECHANISMS OF ITS DEVELOPMENT IN THE ELDERLY

Multimorbidity is currently the greatest medical burden, and it is predicted to increase relentlessly as our population ages [105, 106]. Although multimorbidity seems not to be limited to older adults, many of the most prevalent chronic diseases, including ischemic heart disease, chronic obstructive pulmonary disease (COPD), osteoarthritis, type two diabetes, renal disease, metabolic syndrome and dementia often co-occur with advanced aging [107]. To illustrate, a cross-sectional study by Barnett et al. [105] including 1.7 million patients reported that 30.4% of the patients aged between 45 and 64, 64.9% of the patients aged between 65 and 84 and 81.5% of the patients aged 85 and older have at least two chronic conditions . This suggests that aging represents the major risk factor for the development of multiple chronic diseases, and that there might be common pathways linking chronic diseases related to aging.

A recent study by Barnes [107] identified shared common mechanisms of aging that may connect chronic diseases. Among these mechanisms there seems to be evidence for cellular aging including telomere shortening [108, 109]. Normal aging goes along with telomere shortening, however this shortening seems to be greater in patients suffering from cardiovascular disease, diabetes mellitus and chronic obstructive pulmonary disease. It has been hypothesized that oxidative stress directly causes telomere shortening and impairs telomerase activity, an enzyme that maintains telomere length [108-110]. However, the exact mechanisms that cause telomere shortening in association with the presence of these chronic diseases are still unclear. Besides, cellular senescence, leading to cell apoptosis and signaling of the mammalian target of the rapamycin (mTOR) pathway which regulates cell growth, cell proliferation, transcription and survival, seems to play an important role in aging and its association with chronic diseases and multimorbidity [107]. Furthermore, mitochondrial dysfunction, stem cell exhaustion, epigenetic changes and abnormal microRNA changes have been demonstrated to be underlying mechanisms that may contribute to the development of multimorbidity in older adults (Figure 8). In addition, Barnes et al. [107] suggest that all these molecular mechanisms

and thus most chronic diseases are interrelated, as they are associated with an increased inflammatory response. For example, the pro-inflammatory state, which has been found in atherosclerosis, cancer and heart disease, is the result of mitochondrial over-generation of free radicals. Glucose-induced inflammation through oxidative stress in combination with free fatty acids has been found to be involved in insulin resistance and type two diabetes. Moreover obesity, a common shared risk factor of many chronic diseases, is associated with Reactive Oxygen Species (ROS), resulting in oxidative stress which damages cells and triggers an inflammatory response. All shared molecular mechanisms that are dysregulated and seem to be caused by inflammation in chronic diseases suggest that restoring the inflammatory process could be valuable to reduce the burden of multimorbidity in older adults (Figure 8).

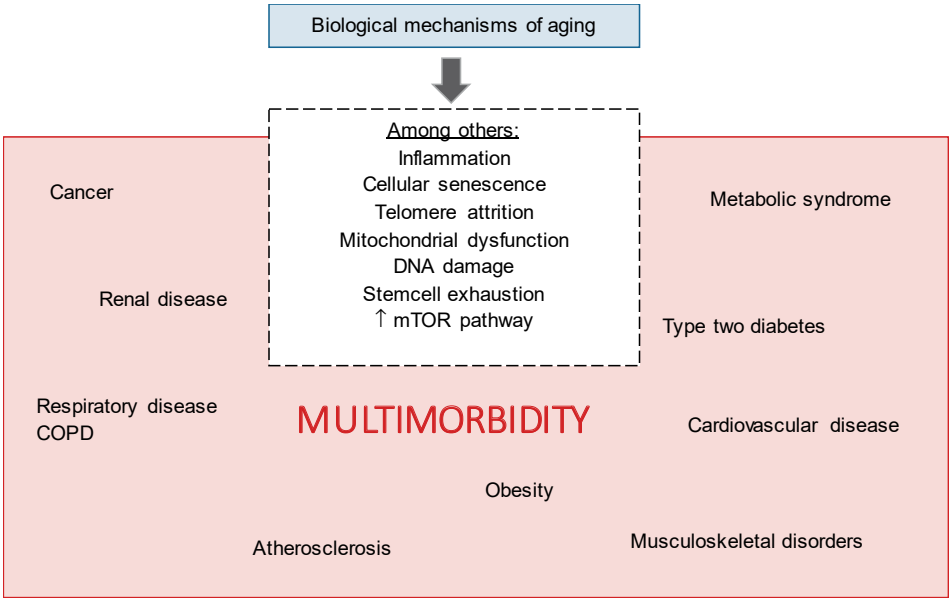


Figure 8. Underlying mechanisms that are the result of advanced aging and are shared between cardiovascular disease, neurological disease, metabolic disease, musculoskeletal disease and cancer.

Possible targets for interventions that reduce inflammation and thereby the mechanisms of accelerated senescence are, besides drugs, lifestyle interventions such as increased physical activity [110-112]. A study by Fleg et al. [111] has already shown that aerobic exercise training has beneficial effects on several age-related biomarkers, and a study by Pinto et al. [112] reports that physical activity induces a rise in systemic levels of cytokines and chemokines with anti-inflammatory properties. Despite discrepancies, Pinto et al. [112] conclude that analysis of the available research confirms the efficacy of regular physical activity as a non-pharmacological therapy against chronic low-grade

inflammation. Physical activity is thus an established lifestyle intervention that has proven its protective and beneficial effects on atherosclerosis, colon and breast cancer [113, 114], ischemic heart disease [115], heart failure [115, 116], type two diabetes [116] and chronic obstructive pulmonary disease [117].

These recent findings are of great importance when we appreciate that the musculoskeletal system is the largest organ or our body, and therefore the general aim of this dissertation is to investigate the association between multimorbidity and physical activity.

AIMS OF THIS THESIS

General aim

The general aim of this dissertation is to study the association between multimorbidity and physical activity and to offer recommendations for targeting patient treatment.

Specific aims

PART 1: PHYSICAL ACTIVITY AS OUTCOME IN MULTIMORBIDITY TREATMENT

The first part of this dissertation concentrates on physical activity as outcome in multimorbidity treatment. Patients with intermittent claudication (index disease) and comorbidity who are referred to the physical therapist or directly access physical therapy care are the central point.

1. To elucidate the complexity of using single-disease guidelines to improve walking distance in patients with intermittent claudication and comorbidity, the **first aim** of the present thesis is to discuss the discrepancy between single-disease guidelines and multiple-diseased patients (Chapter 2).
2. After our recapitalization of the challenges of comorbidity in current physical therapy practice we want to shed light on the current treatment of patients with intermittent claudication and comorbidity in usual physiotherapy care, which has to our knowledge never been done before. Therefore, the **second aim** of this dissertation is to assess whether physiotherapists make reasoned adaptations to evidence-based treatment recommendations when comorbidity influences the single-disease treatment (Chapter 3).
3. We hypothesize that physical therapists may adapt the evidence-based recommendation for intermittent claudication, because comorbidity might influence physical therapy treatment progress and treatment outcome. Therefore, the **third aim** of this thesis is to investigate the association between age, gender, body-mass index, smoking behavior, orthopedic comorbidity, neurologic comorbidity, cardiac comorbidity, vascular comorbidity, pulmonic comorbidity, internal comorbidity and initial claudication distance during and after supervised exercise therapy at 1, 3, 6 and 12 months in a large sample of 2,295 patients with intermittent claudication (Chapter 4). The large sample size of our cohort allows us to be one of a kind and to use a multilevel model to acknowledge that patients receive treatment by different physical therapists.

4. We presume that expected treatment effects shown in research of supervised exercise therapy fall short in physical therapists since the better and healthier patients are often assumed to be included in randomized controlled trials. Consequently, the **fourth** novel **aim** of this thesis is to make a comparison between data on baseline characteristics and treatment response of supervised exercise therapy derived from randomized controlled trial participants and people treated in usual physiotherapy care, who are suffering from intermittent claudication (Chapter 5).

PART 2: PHYSICAL ACTIVITY AND MULTIMORBIDITY IN DAILY LIFE

The second part of this dissertation focuses on the association between daily leisure-time physical activity and multimorbidity. Once patients with comorbidity finalize physical therapy treatment, it is important that adequate physical activity levels are maintained in daily life. Respective the growing amount of patients with multimorbidity, we question whether it is possible to determine who will present maintenance problems concerning optimal day-to-day physical activity levels.

5. We start by conducting the first study in the field of multimorbidity research that associates clusters of multimorbidity with an outcome measure, in this instance compliance with the Dutch physical activity guideline. Therefore, the **fifth aim** of this thesis is to identify clusters of multimorbidity associated with physical activity based on the assessment of a large primary care population (Chapter 6).
6. Since, the majority of patients with co-occurring diseases suffer from the presence of two chronic diseases simultaneously, we are curious about which chronic disease pairs are associated with non-compliance with the Dutch physical activity guideline. We add a second completely new layer to the field of multimorbidity research to our investigation and additionally assess whether having the combination of two diseases leads to even worse physical activity levels than would be expected based on the effect of the diseases individually. The **sixth aim** of this thesis is therefore to assess the synergistic effect of chronic disease pairs on physical activity in a large primary care population (Chapter 7).
7. We decide to finalize this dissertation with a novelty in the research area of multimorbidity *and* physical activity. Therefore, our **seventh aim** was to compile a multimorbidity physical activity behavior profile model, including measurements of fifteen chronic diseases and seven different physical activity types, at once into a latent profile class model (Chapter 8).

STRUCTURE AND OUTLINE OF THIS THESIS

PART 1: PHYSICAL ACTIVITY AS OUTCOME IN MULTIMORBIDITY TREATMENT

The first part of this thesis looks at the role of comorbidity in physical activity treatment. Patients with comorbidity who are referred to the physiotherapist or directly access physiotherapy care for the treatment of the index disease intermittent claudication are the main focus. Chapter 2 discusses how physiotherapists who care for older adults with comorbidity strive to find a balance between adhering to single-disease guideline recommendations and adjusting these recommendations to individual patient circumstances in case of comorbidity. Because most Dutch physical therapy guideline recommendations do not take account of comorbidity, it remains unknown how patients with comorbidity are treated in daily practice. Therefore, by means of a vignette design, the actual treatment of patients with comorbidity in usual physical therapy care will be assessed in Chapter 3. Besides the fact that treatment plans might need to be adapted in case of comorbidity, we hypothesize that comorbidity also affects the effectiveness of physical therapy treatment. In Chapter 4 we will explore which patient variables and comorbidities negatively influence treatment outcome in patients with intermittent claudication. Since we hypothesize that comorbidity influences treatment effectiveness, we suggest there is a discrepancy between treatment effectiveness found in randomized controlled trials and in standard physical therapy care, because mostly only the 'better and healthier' patients are included in clinical trials. In Chapter 5 we will study the degree and impact of patient selection in randomized controlled trials by comparing patient characteristics and treatment outcomes of randomized controlled trials on supervised exercise therapy in patients suffering from intermittent claudication with patients suffering from intermittent claudication who received supervised exercise therapy in the context of usual physiotherapy care, at baseline and after three and six months.

PART 2: PHYSICAL ACTVIVITY AND MULTIMORBIDITY IN DAILY LIFE

Once a patient finishes physical therapy treatment it is important that adequate physical activity levels are maintained in daily life, and therefore the second part of this thesis focuses on physical activity in daily life. To stimulate patients to initiate or maintain physical activity, it is important to develop insights into the association between specific disease combinations and physical activity. In Chapter 6 the association between multimorbidity clusters and physical activity is highlighted. Since most patients with multimorbidity suffer from the presence of two chronic diseases simultaneously and chronic disease pairs provide the basis for clinical understanding how diseases combine togeth-

er and how they are associated with physical activity, in Chapter 7 we will study the synergistic effects of chronic disease pairs on physical activity. This thesis will conclude with multimorbidity-physical activity behavior profiles that are presented in Chapter 8. Latent profile analysis will be used, including both chronic disease variables and physical activity variables in once to develop a multimorbidity- physical activity behavior profile model. Chapter 9 will include a general discussion of our main findings, a critical appraisal related to the primary aim of this dissertation and suggestions for future research in this area.

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Chapter 2

Difficulties of using single-disease guidelines to treat patients with multiple diseases

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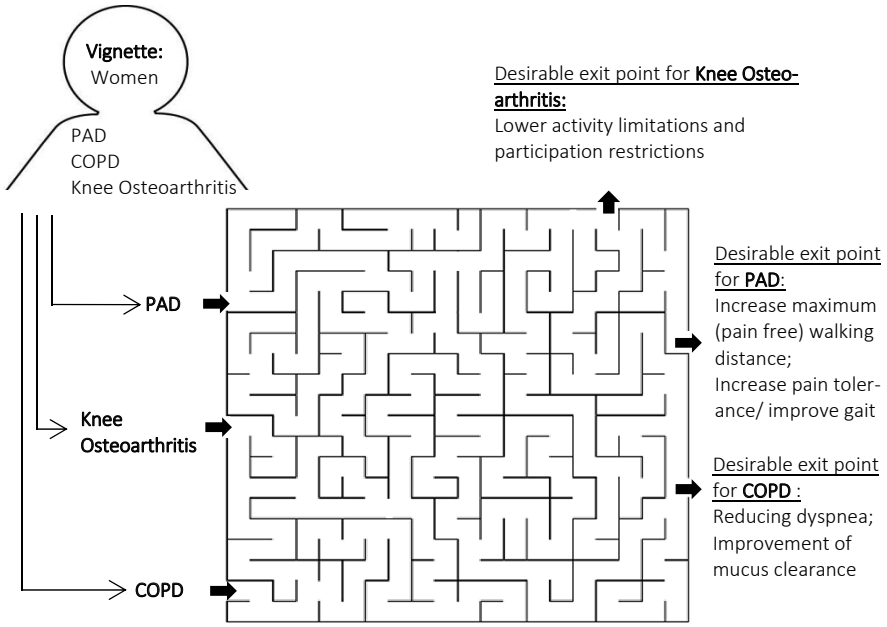
DIFFICULTIES OF USING SINGLE-DISEASE GUIDELINES TO TREAT PATIENTS WITH MULTIPLE DISEASES

Discipline- and disease-specific medical care is increasingly underpinned by evidence-based guidelines. The main goal of these guidelines is to give the best available diagnostic and treatment advice, to decrease variability in daily clinical practice, to reduce inappropriate practice and to improve cost-effectiveness, ideally resulting in better health outcomes for patients [1]. For example, the Royal Dutch Society for Physical Therapy (KNGF) and the Dutch College of General Practitioners (NHG) have published 17 and 96 disease-specific guidelines, respectively, all with the aim of providing a stronger scientific foundation and improve health care [2, 3]. However, the majority of patients (40% at the age of 50 and at least two-thirds of the octogenarian population [4]) simultaneously suffer from multiple medical problems. Caregivers therefore need to consider single-disease evidence contained in a guideline in the view of other relevant guidelines. In this matter Hurwitz et al. [5] already warned that guidelines may encourage users to apply recommendations *'rigidly or unthinkingly',* even in situations where departure from a guideline would be desirable, as might be the case with multimorbidity. Thus, when treating multi-diseased patients, physical therapists themselves have to design a customised treatment plan based on guidelines developed for patients with only one disease and in consideration of the impact of multimorbidity. Once a patient with multimorbidity is admitted to a physical therapy practice, the physical therapist may consider multiple treatment paths. This situation could be compared with a maze: a complex branching passage with many different pathways. To solve the maze, the physical therapist must find a route to travel from start to finish.

THE MAZE OF MULTIMORBIDITY

The maze of multimorbidity could be entered at different points based on the disease (e.g. type, severity) and the health needs for which the patient has been referred to the physical therapist.



Abbreviations: PAD: Peripheral Arterial Disease; COPD: Chronic Obstructive Pulmonary Disease

Figure 1. The Maze of Multimorbidity.

Imagine that a patient with Intermittent Claudication (a symptom of Peripheral Arterial Disease (PAD); see vignette in Figure 1) was not referred to the physical therapist for the treatment of peripheral arterial disease, but by a pulmonologist for the treatment of chronic obstructive pulmonary disease (COPD). Consequently, the treatment focus would not be aimed at increasing the maximum walking distance, but instead at reducing dyspnea and improving mucus clearance.

The maze of multimorbidity also has different final and intermediate *exit* points (i.e. desired treatment outcomes). The final outcome is set by the disease for which the patient was referred. For example, if a patient with peripheral arterial disease visits the physical therapist with the aim to increase the maximum walking distance, the desirable outcome of physical therapy treatment could be an increase in metres that the patient can walk. Imagine that this patient would be hindered while walking by shortness of breath due to chronic obstructive pulmonary disease. Then the intermediate goal for physical therapy care would be an improvement in breathing techniques. After the breathing problems have been reduced, the physical therapist may continue treating the index disease peripheral arterial disease. If the physical therapist continues treating the patient without taking heed of the observed shortness of breath, the patient will never reach the desired treatment outcome. The patient will always be hindered at the same point because he or she is walking into a dead end due to limitations related to chronic obstructive pulmonary disease.

EXPERIENCE-BASED EVIDENCE: A SOLUTION IN CASES OF MULTIMORBIDITY?

The maze metaphor illustrates that clinical decisions in physical therapy require considering a discrete range of choices from which the physical therapist will select the most appropriate treatment or intervention to meet a patient's specific needs. Ideally, we make these choices based on the highest value of level 1a evidence from research. However, complex patients suffering from multimorbidity are under-represented in systematic reviews and randomised controlled trials because their presence presents methodological challenges [6]. Hence, collecting evidence on all possible disease combinations might even be an impossible endeavour. The high level of heterogeneity in the study population would require researchers to recruit impossibly large study populations. Taking into account loss to follow-up and drop-out rates, required sample sizes will enlarge.

How to proceed from here? Relying on experience-based evidence might be an option, to underpin current practice [7]. For example Moitra et al. [8] elaborated on the impossibility to perform large epidemiological studies in case of perioperative cardiac arrest, a disease that occurs rarely, has a heterogeneous spectrum of causes and is distinct from cardiac arrest in other settings. The authors highlighted that from a practical point of view it is not feasible to avoid anaesthesia during surgical manipulation in order to be able to investigate the contribution of anaesthesia to cardiac arrest. However, among anaesthesiologists there is much expertise and experience in managing cardiac arrest in perioperative patients and thus experience-based evidence should be cherished in the generation of protocols. But, relying on care providers experience has also raised discussion in many different fields in medicine [8, 9, 10]. Rinchuse et al. [7], for instance, from the field of Orthodontic and Dentofacial Orthopedics, warned for incautiously trusting personal perceptions (empiricism), highly respected people (authority), intuitively appealing logical ideas (rationalism) and long held beliefs (tenacity). Although these pitfalls exist, Leape et al. [9] from the field of Health Policy and Management, stated there will never be complete evidence for everything, but that the alternative is to make reasonable judgements based on best available evidence in combination with successful experiences in health care.

Acknowledging the pitfalls of experience-based information, it may be helpful when large numbers of data are collected and analysed in a systematic way. In general, identifying the specific influence of comorbidities on treatment outcome, in addition to considering physical therapists' experiences working with these patients in the past, may enable us to identify possible alternations of treatment for these patient groups and therefore improve treatment success. Health professionals gradually acquire experiences that enable them to make implicit connections between patients who need to be treated and patients they have seen in the past. In the context of systematically gathered experience-based evidence, curve matching may be a powerful approach that can enhance the

memory of health professionals by putting existing information (i.e. electronic medical record data collections) to a new use. The key idea is to find relevant historic data about patients that are similar to the new patient and to use this data to suggest the treatment outcome of the new patient [6, 11]. This approach takes into account the uniqueness of patients by including individual patient characteristics and specific disease combinations in the treatment outcome determination. It gives physical therapists' the opportunity to customise medical treatments for individual patients. Hence, putting existing information to a new and systematic use may help to guide physical therapists' through the complex process of managing patients with multimorbidity.

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Chapter 3

Comorbidity forces physiotherapists to deviate from guideline recommendations resulting in various treatments for the same patient:
a Vignette study

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ABSTRACT

Rational, aims and objectives:

The aim of this Vignette study was to assess whether physical therapists make reasoned adaptations to evidence based treatment recommendations when comorbidity influences the single disease treatment.

Method:

To study the influence of comorbidity on treatment recommendations, three vignettes were created based on authentic patient data. In the first vignette a single-diseased intermittent claudication patient was described, in the second comorbidity chronic obstructive pulmonary disease was added and in the third vignette additionally knee osteoarthritis was added. Therapists described three treatment plans and their decision rationale. A random selection of 100 Dutch Claudication Network members was invited to participate in this qualitative study.

Results:

Response rate was 61%. Thirty percent of the physical therapists did not adjust treatment despite comorbidity. Another 30% partly adapted the treatment plan when comorbidity was added to the vignette. The presence of comorbidity induced 40% to abandon guideline recommendations and to create an individualised treatment plan based on the health needs of the vignette patient.

Conclusion:

This study showed that the majority of physical therapists makes adaptations to evidence-based recommendations when comorbidity is present. However, the same patient was treated in various ways by different physical therapists.

INTRODUCTION

Physical therapy guidelines are systematic and evidence-based statements designed to help physical therapists to make decisions about treatment options. Although they provide detailed guidance for managing patients with single diseases, they generally disregard comorbidity. The exclusion of guidance in case of comorbidity makes the applicability of these guidelines questionable [1]. Boyd and Fortin [2] showed that applying diverse clinical practice guidelines to a hypothetical 79 year old woman with multimorbidity leads to a complex and even potentially harmful treatment regimen. The patient would have been prescribed 12 types of medication used in 19 doses per day and had to follow 14 non-pharmacologic treatments (e.g. diet, exercise, healthcare visits and laboratory testing). This example illustrated the incompatibility between evidence-based guidelines and what is actually happening in real life.

How patients with comorbidity are treated in daily practice is unknown. Understanding the decision making process of physical therapists and exploring the treatment of comorbid patients in daily practice might be a first step to unravel the complexity of treating multi-diseased patients. In this study, we examined the impact of the comorbidities chronic obstructive pulmonary disease and knee osteoarthritis [3, 4] on treatment recommendation in a hypothetical 69 year old woman with the index disease intermittent claudication (vignette). Conformity between individual treatment plans for the vignette patient was investigated. Moreover, whether therapists' characteristics impacted the way physical therapists think about treatment decisions, actual treatment modalities employed and the treatment rationale was studied. The aim of this study was to open the black box and to identify the treatment of patients with comorbidity in daily physical therapy practice.

The research questions were:

1. Do physical therapists make reasoned adaptations to evidence based treatment recommendations when comorbidity influences the single diseases treatment approach?
2. Do physical therapists' characteristics (age, gender and experience in treating patients with intermittent claudication) influence treatment recommendations made in patients with comorbidity?

METHODS

Design

Impact of comorbidity and therapists' characteristics on treatment recommendations was studied using a patient vignette. The vignette was accompanied by an open-ended questionnaire which consisted of three parts. In each part, a description of the same vignette was given. Demographic characteristics, medical and medication history and treatment goals were described. Using a step-up approach, two common comorbidities, chronic obstructive pulmonary disease and knee osteoarthritis [3, 4] were sequentially added to the vignette. In all three parts of the questionnaire, intermittent claudication was the index-disease for which the patient was referred to the physical therapist. In vignette one, the patient solely had intermittent claudication. In vignette two the same patient was described as additionally having chronic obstructive pulmonary disease stage Gold III. In vignette three, the patient suffered from intermittent claudication, chronic obstructive pulmonary disease and knee osteoarthritis. Therapists were asked to determine a treatment plan in which exercise length, intensity, mode, density, type and progression was described. For each element of the treatment plan they were asked to record their underlying treatment rationale.

Creating the vignettes

To ensure that the vignettes were representing real life practice, patient data from an existing prospective intermittent claudication cohort (*N*=528) were used. All cohort patients with more than two comorbidities were selected. Based on recent literature, a selection was made of combinations of comorbidities for which there is evidence that they impede intermittent claudication treatment [4-6]. The selected patient was female, 69 years old, suffering from chronic obstructive pulmonary disease and knee osteoarthritis as comorbid diseases. Demographic characteristics, medical history, information about medication and treatment goals of this patient as described in the cohort were used for the patient description. The profile of the patient was anonymised, meaning that a fictitious name (Mrs Jansen) and photo were added to the patient description. Portrait right was obtained.

Verifying the vignettes

The patient description was verified by a team of medical professionals: a sports physician/physical therapist, a pulmonologist, a vascular surgeon and a nurse practitioner. Completeness of medical information, symptoms described and the appropriateness of medication were discussed in individual meetings. All meetings were audiotaped. After each meeting, the patient description was adjusted and discussions took place until no

new insights appeared. The representativeness of the vignettes was investigated in individual discussions between the primary investigator and three randomly selected physical therapists of the Dutch Claudication Network (ClaudicatioNet), specialised in the treatment of patients with intermittent claudication.

Participants

All 1497 members of the Dutch Claudication Network (ClaudicatioNet) were mailed to join this study within three days. This was done to restrict the number of responders since our study was qualitative in nature. Within three days 187 responded. Since experience is an important modifier when investigating health outcomes [7], all responders were asked to indicate their number of treated intermittent claudication patients. Therapists were consequently divided over three strata; <5; 5-25 and >25 treated patients over the past two years. Random sampling of 100 therapists was applied within each stratum, therewith assuring that the samples fall between Creswell's [8] suggested range of 20 to 30 for achieving saturation in qualitative questionnaires. Due to the lower amount of most experienced physical therapist among initial responders and the threshold needed to achieve saturation, the researchers decided to compare the two more experienced strata (5-25 and >25) with the less experienced stratum (<5). Therefore, 100 therapists were randomly selected from both groups. Age and gender were also registered. Participants were compensated (by professional accreditation points) to stimulate completeness and quality of response. Detailed information about the required sample size and data saturation can be found in the E-method.

Table 1. Distribution of physical therapists before and after random sampling

	Before randomisation	After randomisation
Group A (treated less than 5 patients with intermittent claudication during the last two years)	79	50
Group B (treated between 5 and 25 patients with intermittent claudication during the last two years)	147	32
Group C (treated more than 25 patients with intermittent claudication during the last two years)	18	18

The questionnaire was made in Adobe X and distributed online. In addition to the questionnaire, all physical therapists received information on: the purpose of the questions; the intended target group; how collected data would be used; the confidentiality of the answers and a deadline for completion and instructions for returning the questionnaire. Therapists had two weeks to return the questionnaire and a reminder was sent by email one week thereafter.

Data analysis

An inductive approach was used to analyse the qualitative data. Data coding and organization was used as primary process for developing themes and encoding these themes prior to interpretation. Themes were developed according to grounded theory rooted in the qualitative data set themselves [9]. First data was read and then possible themes were identified. Next, identified themes were compared and contrasted. Finally, a theoretical model was built [10]. Data analysis control took place by one physical therapy expert (R.B) and one non-expert (I.M). All information was reviewed and independently the appropriateness of major identified themes was checked. The whole theme development was done using a consensus approach, meaning that whenever divergent interpretations occurred, transcripts were reviewed and discussed until consensus was reached.

RESULTS

Overall response rate was 61%; in the less experienced group 56% and in the more experienced group 66%. In vignette one, Mrs Jansen was described as a single-diseased intermittent claudication patient and all therapists based their treatment plan on the guideline intermittent claudication of the Royal Dutch Society for Physical Therapy (KNGF). Most frequently mentioned rationales supporting the adherence to this guideline recommendation were: no indication that deviation from the guideline was necessary, positive previous experiences, physiological mechanisms, the health needs of the patient and financial constraints. To illustrate: *"this is the exercise frequency as described in the KNGF guideline Intermittent Claudication"; "both literature and my personal experience showed that three times a week exercising is most effective in patients with intermittent claudication"; "because of physiological mechanisms"; "treatment recommendation described in the guideline is most efficiently related to the health needs of the patient and Mrs Jansen can experience results quickly"; "this is the amount of training that is compensated by insurance companies"*. Age, gender and patient volume in treating patients with intermittent claudication did not influence physical therapy treatment recommendation.

In vignette two chronic obstructive pulmonary disease Gold stage III was added to the patient description and in vignette three, knee osteoarthritis was added as second comorbid disorder. For both vignettes three types of responses were noted: (1) Unadjusted intermittent claudication treatment despite comorbidity; (2) Partial adaptation because of comorbidity; and (3) Individualised treatment due to comorbidity.

(1) Unadjusted intermittent claudication treatment despite comorbidity

Thirty percent of the physical therapists reported not to adjust treatment. Themes mentioned were: Trust in KNGF guideline recommendations for intermittent claudication and chronic obstructive pulmonary disease, evidence from literature, physiological mechanisms, financial constraints, practicalities and the perceived health needs of the patient. Therapists indicated *"treatment focus is the improvement of maximum walking distance and exercises performed to reach this effect will also be beneficial for chronic obstructive pulmonary disease"; "30 minutes is the treatment duration that is reimbursed by insurance companies and I will have to stick to this".* Often it was mentioned that the treatment plan described for vignette two was also executable for patients with knee osteoarthritis and that the presence of knee osteoarthritis did not require treatment adaptation. To illustrate an extreme case, one therapist indicated *"knee pain during supervised exercise therapy will be acceptable because of the fact that the patient will receive a new knee anyway".*

(2) Partial adaptation because of comorbidity

Another 30% of all physical therapists partly adapted the treatment plan when comorbidity was added to the vignette. For some treatment features physical therapists agreed on the direction of change, for others they deviated (Table 2).

Table 2. Treatment features on which physical therapists agreed or disagreed on the direction of change due to comorbidity

Treatment features on which physical therapists coincide on the direction of change	Treatment features on which physical therapists disagree on the direction of change
• Exercise intensity	• Exercise frequency
• Exercise density	• Exercise mode
• Exercise type	• Exercise length

Therapists agreed on reducing exercise intensity in the presence of chronic obstructive pulmonary disease. To illustrate "if exercise intensity is too high, the patient will be restricted by chronic obstructive pulmonary disease"; "Chronic obstructive pulmonary disease should not be the hindering factor to stop walking, therefore, exercise intensity needs to be decreased". Furthermore, agreement existed regarding exercise density. For interval training most physical therapists indicated that the patient should train three to five minutes and subsequently should rest between two and four minutes. Themes mentioned were financial constraints and positive experiences with this exercise density. Therapists that choose endurance training indicated to start with 10-15 minutes walking ultimately aiming at increasing walking time to 30-60 minutes. This was motivated by the KNGF guideline recommendations for intermittent claudication and

chronic obstructive pulmonary disease, the patient health needs and positive previous experiences. Physical therapists also agreed on the exercise type used during supervised exercise therapy. Therapists agreed that despite comorbidity it may be feasible to perform walking exercises and that the treadmill offers the possibility to define walking distance, speed and slope in a way that makes it possible to optimally train intermittent claudication despite chronic obstructive pulmonary disease and knee osteoarthritis. Also cycling was indicated as a valid exercise type for intermittent claudication patients with comorbidity. Motivations for this decision are: "cycling is less burdensome for chronic obstructive pulmonary disease"; "it's good to improve the overall condition of the patient"; "it has a positive influence on walking distance as well as breathing problems"; "it can help to reduce body weight of the patient" and "it is easier for the patient to start with cycling compared to walking."

Opinions deviated regarding the adaptation of exercise frequency. Some therapists claimed that supervised exercise therapy once or twice a week is enough workload for an patient with intermittent claudication and comorbidity, while another group stated that supervised exercise therapy three times a week would be preferable. Reduced exercise frequency was motivated by reduced expectations regarding the ability to exercise and that a higher frequency would lead to more knee problems. Considerations for three times a week supervised exercise therapy were: (1) *"to reach a cardiopulmonary training effect"*; (2) *"KNGF guideline recommendations for intermittent claudication and chronic obstructive pulmonary disease"*; (3) *"more 'in house treatment' to control for desaturation during exercise, which is not possible in the home situation"* and; (4) *"facilitating exercise routines becomes even more important in chronic obstructive pulmonary disease patients".* Moreover, physical therapists disagreed on exercise modes in the presence of comorbidity. Central themes to determine exercise mode were presence of chronic obstructive pulmonary disease and expectations regarding the patients' ability to exercise. No clear pattern could be distinguished whether endurance or interval training was preferred. Arguments for interval training were: *"because of breathing problems it will not be possible for the patient to participate in endurance training"* and *"endurance training will promote dyspnoea"*. Endurance training was preferred for the following rationales: *"endurance training will improve cardiopulmonary capacity"* and *"endurance training is most effective for increasing VO2max and walking distance"*. Further, physical therapists disagreed on exercise duration. Therapists trained the intermittent claudication patient with comorbidity either for 30 minutes or 60 minutes. Rationales for 30 minutes supervised exercise therapy were grounded on reimbursement schemes and reduced physical capacity of the patient: *"this is the regular treatment duration that is reimbursed"; "this patient has to get used to exercising"; "Mrs Jansen has a restricted physical capacity"; "it is a combination of the guideline intermittent claudication and chronic obstructive pulmonary disease"* and *"it is the most effective duration to increase aerobic capacity".* Treatment duration of 60 minutes was moti-

vated by the opportunity to integrate exercises for each disease. Reasons for 60 minutes of supervised exercise therapy were: (1) "*to be able to treat more different components within 60 minutes, such as muscle strength training for the whole body";* (2) *"sputum mobilisation, breathing techniques and stability training for the knee need to be included in the treatment plan";* (3) *"there is enough time for condition and endurance training";* (4) *"training on a treadmill already takes 20-30 minutes, but additional increase in muscle strength is needed"* and (5) *"it is important that the patients get enough rest in between two exercise series".*

(3) Individualised treatment due to comorbidity

The presence of the comorbidities chronic obstructive pulmonary disease and knee osteoarthritis forced 40% of the participating physical therapists to abandon guideline recommendations and to create an individualised treatment plan. This group solved the problem of inadequate reimbursement by treating patients in groups of two or more. By combining the treatment of two or more patients, the total treatment duration increases and as a consequence more time is available to: (1) include exercises for each disease in the supervised exercise therapy protocol; (2) to allow the patient enough rest and; (3) to educate the patient. Therapists mentioned *"this exercise length makes it possible to give endurance training as well as muscle strength exercise and have time to provide information"; "the combination of intermittent claudication, chronic obstructive pulmonary disease and knee osteoarthritis requires a more extensive treatment plan. One hour is needed to cover all three diseases in the training"*. In addition, one therapist indicated to involve a colleague with chronic obstructive pulmonary disease expertise in the decision making process to optimize care for Mrs Jansen. Another physical therapist circumvented hindrance by knee osteoarthritis during walking on a treadmill; *"by using a kinesiotape I will be able to keep the exercise frequency high enough to reach a cardiopulmonary effect, but also to take care of the knee".*

An overview of therapists' considerations regarding the treatment of patients with intermittent claudication and comorbidity is given in Figure 1. On the x-as the three vignettes are listed. The y-as describes treatment complexity. This figure shows that in the absence of comorbidity physical therapists followed the KNGF guideline intermittent claudication to determine the optimal treatment plan of Mrs Jansen. Adding chronic obstructive pulmonary disease, to the patient description resulted in additional considerations. First, adaptability of the treadmill protocol was indicated to be important. This allowed changing exercise intensity thereby facilitating that leg pain and not breathing problems would be the reason to stop walking. Second, additional activities like breathing exercises were added to the treatment plan. Third, the presence of comorbidity might restrict the desired treatment outcome. Adequate treatment structure and communication between therapist and patient seemed crucial to facilitate

effective care and to avoid misconceptions. Day to day adaptation of the treatment plan may be necessary due to chronic obstructive pulmonary disease complaints influenced by humidity and temperature changes. Fourth, medication interaction needed to be taken into consideration when treating an intermittent claudication patient with comorbidity chronic obstructive pulmonary disease. Additionally, chronic obstructive pulmonary disease may decrease the exercise capacity and workload of the patient necessitating adaptation of exercise intensity. Fifth, physical therapists mentioned that constant control of the saturation of the patient was important.

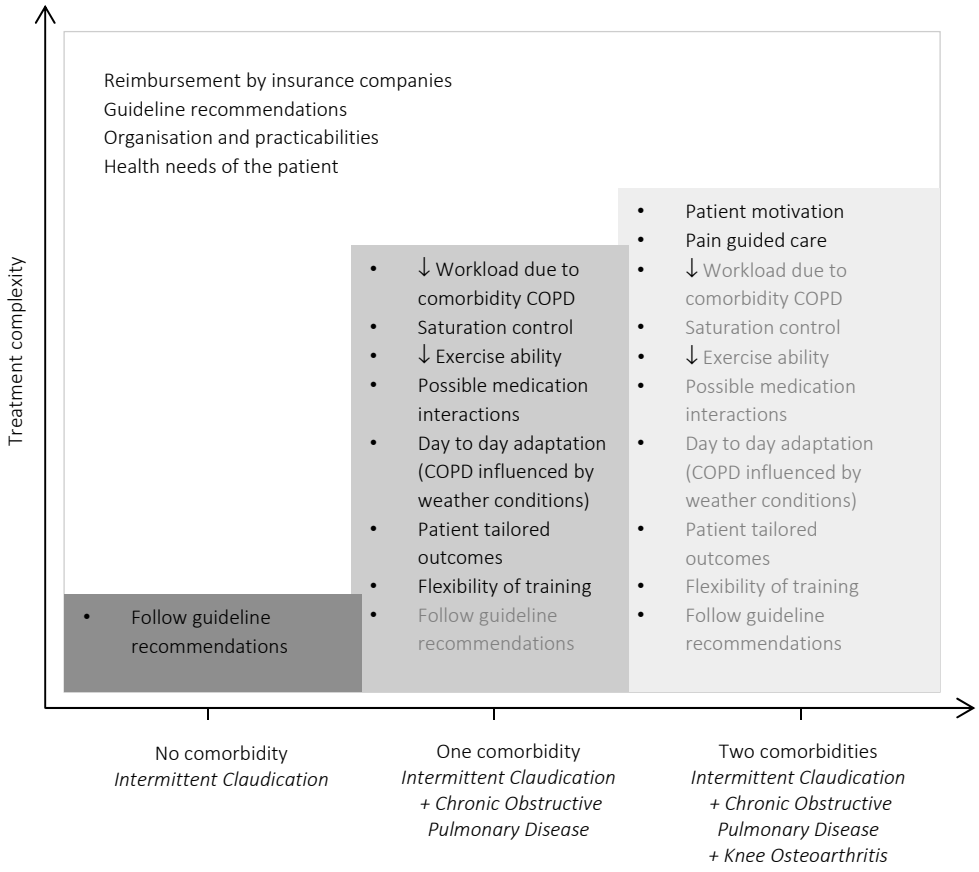

Figure 1. Therapists considerations regarding the treatment of patients with intermittent claudication with and without comorbidity

Pain guided care was mentioned as an important additional consideration to determine treatment, when osteoarthritis was added. Also, patient motivation played an important role. The underlying aim of physical therapy is that patients maintain exercising. Aspects that influence treatment determination regardless of the presence of comor-

bidity were reimbursement policies of insurance companies, guideline recommendations, organisation and practicalities (clinic schedule, training in groups) and the health needs of the patient. Results showed that an increase in the number of comorbidities leads to an increase in treatment complexity (Figure 1).

DISCUSSION

An effective physical therapist should be able to identify health problems, seek for the cause of the problems and plan specific treatments with a sound rationale [10]. Regarding the treatment of intermittent claudication patients with comorbidities, three treatment trends could be distinguished.

The first trend was unadjusted intermittent claudication treatment ignoring comorbidity. Literature showed that strict adherence to clinical practice guidelines might introduce problems when treating patients suffering from comorbidity. Treatment of one disease might interact negatively with the treatment or natural course of a co-existing disease. For example walking exercises may be beneficial for intermittent claudication and chronic obstructive pulmonary disease, but may worsen osteoarthritis severity [11]. Reimbursement, practicalities and/or organisational issues were often mentioned as factors impeding treatment adaptation when comorbidity was present. Recent literature suggested that having comorbidity was associated with more healthcare service utilization and higher costs. The growing amount of multimorbid patients indirectly requires further investigation to determine management approaches that allow physical therapists and other professionals to optimize care for patients with comorbidity.

The second trend is partial adaptation of the intermittent claudication guideline. The results showed that therapists adapted various features of the treatment plan when comorbidity was present. Factors being adapted varied between therapists. Literature showed that patients suffering from chronic obstructive pulmonary disease were hampered by functional impairment evidenced by lower walking capacity and reduced cycling endurance [13]. Moreover, leg discomfort was more and more seen as a frequent exercise-limiting symptom and Debigarè and Maltais [14] revealed that lower limb muscles in chronic obstructive pulmonary disease patients were atrophied, weak, fatiguable and metabolically inefficient. Therefore, the presence of chronic obstructive pulmonary disease as comorbidity influenced walking exercises that were normally performed by intermittent claudication patients. Regarding knee osteoarthritis, Mangione et al. [15] assumed that premature termination of exercise because of knee pain may prevent people from training at sufficient duration and intensity to achieve training adaptations. This implies that adaptations need to be made in multi-diseased patients to be able to reach the treatment goals and to improve patient's health needs. However, which

treatment features need to be adjusted with existing comorbidity is lacking and consequently, treatment adaptations seen in the results of this study cannot be judged.
The third trend is called 'patient-specific treatment.' Physical therapists tried to create an individualised treatment plan based on patient health needs, integrating existing comorbidities. To circumvent financial constraints and practicalities therapists combine the treatment of similarly diseased patients. As a consequence, treatment duration increases which allows a more patient-centred approach including specific components for each disease. These individualised treatment approaches are in line with recent literature on treatment of comorbid patients. For example, a study of Starfield et al [16] described that the treatment needs to focus on a patient-centred approach and that the integration of various disease perspectives determines treatment effectiveness. However, which components of a physical therapy treatment plan need to be changed to take comorbidity into consideration was not investigated until now.

Clinical decision making is a component of clinical reasoning and thereby of central importance when determining optimal treatment for patients with comorbidities. Acquiring valid information is the basis of clinical decision making. The safest and most comfortable position for professionals is to follow the treatment course as described in the information resources. This phenomenon is characterised as "pattern recognition" and it is considered to be the lowest level of clinical decision making [17]. Health care professionals identify patterns in patients and look if these patterns are identical or similar to the clinical manifestations of the patients described in the resources. If these patterns match, the described treatment course is applied. Vignette one, describing a single-diseased intermittent claudication patient, invoked most therapists to use the intermittent claudication guideline to determine the treatment plan. Simply put, they treat the patient as is recommended in the guideline. This saves time and allows them to follow instructions provided according to the best evidence available. However, in our vignette we gradually added important uncertainties to the decision-making process in the form of comorbidity. Uncertainty existed regarding both the optimal treatment of the patient described in vignettes two and three, and the treatment outcome belonging to the treatment chosen. The general rate of treatment failure may be known, but in whom it will fail is unpredictable at the time the treatment is initiated. To deal with these uncertainties associated with the decision problem we need to find the best available evidence to support or refute our assumptions. In general, we need to create a framework to organize all of these uncertainties into a coherent way. Evidence-based practice is consistently advocated as a means to improve the quality of clinical practice. The aim of evidence-based practice is to address the problem of clinical practice variation by using standardized practice guidelines [18]. While there are benefits of providing guidelines to therapists regarding the treatment of single-diseased patients, the routine use of standardized recommendations threatens to reduce physical therapists to performing 'cookbook medicine'. Especially, the growing population of elderly

people and the increasing number of people suffering from comorbidity, necessitate a broader perspective on factors influencing decision [19]. In fact, guidelines are written for 10% of the "average" patients and cannot cover the entire variation of patients. Especially, when treating patients with comorbidity, there might be good clinical reasons to deviate from guideline recommendations. Additionally, patients differ in how an illness affects them and in how they respond to treatments.

Limitations

Vignettes were generated in collaboration with professionals working in the field and participants are typically asked to respond to the vignette with what they would do in a particular situation [20]. The use of vignettes is, however, not unproblematic. Using a vignette technique has two main difficulties, namely (1) the difference between real life and vignette response and (2) the difference between self-reported behaviour and actual behaviour. It is important that a vignette is real [20] and relevant [21] to participants, because this may help to account for a close relationship between people's real life and vignette response. Our vignette construct was based on a real patient case and to ensure the representativeness of our described patient case, we verified it with professionals and experts in the field. This verification procedure ensured that the vignette was representative for the group of multimorbid patients in practice. Regarding the relevance of the vignette, we based the selection of comorbidities on recent literature which stated that chronic obstructive pulmonary disease and knee osteoarthritis are common comorbidities seen in patients with intermittent claudication that impede treatment [2]. A study by Hughes [20] described how differences in responses to vignettes may be caused by a gap between what people think should be done and what actually is done in practice. The use of the intermittent claudication guideline as a supporting tool might have influenced our results and thus may have led to a difference between 'should' and 'would' response. In the first vignette, an intermittent claudication patient was described and therapists were asked to write down a treatment plan for this patient. The optimal treatment for a single-diseased intermittent claudication patient is described in the evidence-based intermittent claudication guideline. We did not specify the permission and/or restraint regarding the use of the intermittent claudication guideline for answering our questionnaire. The fundamental reason for doing so was that the aim of this study was not to test the knowledge of therapists, but to see how treatment changes when comorbidity was added to an intermittent claudication patient. Nevertheless, some therapists may have used the guideline to determine the treatment plan, although not doing so in daily practice. Thus, the establishment of a treatment plan for our questionnaire might have deviated from determining treatment of intermittent claudication patients in real practice. Another form of bias could be caused by the fact that therapists had to write down the whole treatment plan (12 months of supervised exercise therapy) at one time point, while in practice treatment

plans are adapted regularly over time. Through treatment different problems will be resolved and new problems will come up and based on this treatment might need to be added or modified as conditions change [22, 23]. Furthermore, in physical therapy it is vital to keep track of how the patient is doing. This way, therapists will know whether treatment is working and whether adaptations need to be made. In this study, physical therapists had to write down the treatment plan for Mrs Jansen at one time point, without knowing the impact and the consequences of this treatment plan. Therapists did not have the possibility to control treatment and make adaptations when necessary, which may be a contrary to daily practice.

If we want to achieve optimal physical therapy care for patients with comorbidity in future, we need to understand and manage the multiplicity of factors that influence treatment choice in multimorbid patients.

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APPENDIX

APPENDIX 1. SAMPLE SIZE AND DATA SATURATION

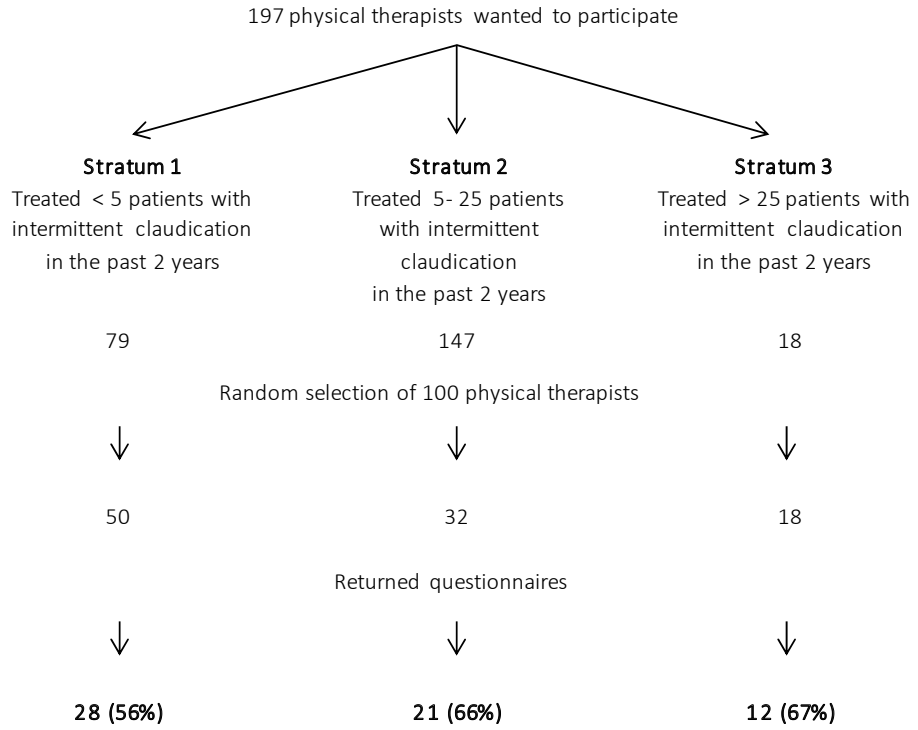

Figure 1. Stratified sampling of research participants based on the amount of patients with intermittent claudication treated during the last two years.

In qualitative questionnaire studies a sample between 20 to 30 participants is required to assure saturation [1]. An observational study of Cook et al. [2] showed that the response rate to postal surveys in studies of healthcare professionals is 56% (95%CI 54% to 58%). Based on this information from the literature, the vignette including the questionnaire was send to 100 physical therapists. Assuming a response rate of approximately 50%, it was concluded that a sample of 100 physical therapists is enough to assure data saturation. The results of this vignette study showed a response rate of 61%, which is significantly higher than was expected. Next to this, in qualitative studies representativeness of data is measured by saturation. During the process of coding all researchers independently assured that saturation was reached.

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Chapter 4

Patient characteristics and comorbidities influence walking distances in symptomatic peripheral arterial disease:
a large one-year retrospective physiotherapy cohort study

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ABSTRACT

Objectives:

The aim of this study is to investigate the association between age, gender, body-mass index, smoking behavior, orthopedic comorbidity, neurologic comorbidity, cardiac comorbidity, vascular comorbidity, pulmonic comorbidity, internal comorbidity and initial claudication distance during and after supervised exercise therapy at 1, 3, 6 and 12 months in a large sample of patients with intermittent claudication.

Methods:

Data was prospectively collected in standard physiotherapy care. Patients received supervised exercise therapy according to the guideline intermittent claudication of the Royal Dutch Society for Physiotherapy. Three-level mixed linear regression analysis was carried out to analyze the association between patient characteristics, comorbidities and initial claudication distance at 1, 3, 6 and 12 months.

Results:

Data from 2995 patients was analyzed. Results showed that being female, advanced age and a high body-mass index were associated with lower initial claudication distance at all-time points ($p= 0.000$). Besides, a negative association between cardiac comorbidity and initial claudication distance was revealed ($p= 0.011$). The interaction time by age, time by body-mass index and time by vascular comorbidity were significantly associated with initial claudication distance ($p\leq 0.05$). Per year increase in age (range: 33-93 years), the reduction in initial claudication distance was 8m after 12 months of supervised exercise therapy. One unit increase in body-mass index (range: 16-44 kg/m^2) led to 10m less improvement in initial claudication distance after 12 months and for vascular comorbidity the reduction in improvement was 85m after 12 months.

Conclusions:

This study reveals that females, patients at advanced age, patients with a high body-mass index and cardiac comorbidity are more likely to show less improvement in initial claudication distance after 1, 3, 6 and 12 months of supervised exercise therapy. Further research should elucidate treatment adaptations that optimize treatment outcomes for these subgroups.

INTRODUCTION

Identifying subgroups of patients who benefit less from physiotherapy treatment is a crucial preparatory step to be able to early adjust treatment expectation and treatment programme. The primary treatment modality for patients with Peripheral Arterial Disease (PAD) is physiotherapy and practice results show a high variety in treatment outcome.

Peripheral Arterial Disease in the leg(s) is a manifestation of narrowing or blockage of arteries (atherosclerosis) that causes poor blood flow to the lower extremities. The clinical spectrum of patients ranges from asymptomatic atherosclerosis to those with the common symptoms of intermittent claudication, e.g. tight, aching, or squeezing pain in the calf, thigh or buttock. Symptoms occur when the delivery of oxygen is inadequate to meet the metabolic requirements of the active skeletal muscle [1]. Leg pain is relieved by rest. Intermittent claudication leads to a moderate or severe impairment in walking ability. In order to improve walking ability, supervised exercise therapy by a physical therapist is recommended as the primary training modality for this patient group [2-4]. Walking limitation is measured by the initial claudication distance, the distance at which the patient experiences the onset of claudication pain and the absolute claudication distance, the distance at which the pain forces the patient to stop walking [3].

A few small scale studies indicate that patient characteristics and comorbid conditions might lead to considerably poorer treatment outcomes during and after supervised exercise therapy [5-10]. For example, Katzel et al. [6] (*N*=141) pointed out that current smokers had a shorter time to onset of claudication pain compared to former or never smokers (188± 28 s vs. 173±25 s and 309± 54 s, respectively; p=0.023). A reduced improvement after conservative treatment by risk factor modification and physical training for female patients (hazard ratio (HR) 0.51; p =0.052) was presented by Amighi et al. [7] (*N*=181). Dolan et al. [8] (*N*=460) observed that after adjusting for age, PAD patients with diabetes type 2 had a shorter mean 6-min walking distance (1,040 vs. 1,168 feet; p<0.001). A recent study of Farah et al. [9] (*N*=415) explored that cardiovascular disease was associated with shorter absolute claudication distance and initial claudication distance (OR=2.45; CI: 1.11-5.39 and OR=1.88; CI: 0.86-4.09, respectively) and age, body-mass index, pulmonary disease and smoking behavior were predictive variables for absolute claudication distance that were presented by Kruidenier et al. [10]. Taken together, from a scientific point of view these studies seem to provide compelling evidence that specific patient characteristics and comorbidity influence physiotherapy treatment success in patients with intermittent claudication. However, all previous investigations were based on small numbers of patients (maximum *N*=460 [7]) largely recruited in the hospital setting. By the use of our large cohort we want to check whether the hampering effects of patient-related variables and comorbidity remain in place in a large population of patients with intermittent claudication that follow super-

vised exercise therapy in the usual care setting. Moreover, the large sample size of our cohort makes it possible to use a multilevel model through which it can be acknowledged that patients received treatment by different physiotherapists [11].

If the results of our large physiotherapy cohort show that the inverse association between patient characteristics and comorbidity (as identified in earlier small scale studies) remains, subgroups of patients that benefit less from supervised exercise therapy can most certainly be identified. The aim of this study is to investigate the association between age, gender, body-mass index, smoking behavior, orthopedic comorbidity, neurologic comorbidity, cardiac comorbidity, vascular comorbidity, pulmonic comorbidity, internal comorbidity and initial claudication distance during and after supervised treadmill exercise at 1, 3, 6 and 12 months in a large physiotherapy cohort study.

METHODS

Study design and setting

To study the association between patient characteristics and comorbidity on initial claudication distance analyses on prospectively collected Electronic Medical Record (EMR) data was performed. Registration of the patients' medical data in the electronic medical record was part of standard physiotherapy care. Data from patients with intermittent claudication that were treated with community-based supervised exercise therapy between 2006 and 2011 was used for this study. The ethics committee/institutional review board 'Medisch Ethische Toetsingscommissie van Atrium Medisch Centrum, Orbis Medisch en Zorgconcern en Zuyd Hogeschool' approved at August, 19th 2013 the present physiotherapy cohort study. Data was gathered in the context of usual care. All participants signed written informed consent for their clinical records to be used in the present physiotherapy cohort study and patient records/information was anonymized and de-identified prior to analysis (METC number: 13-N-85). To enhance transparency this article is written according to the STROBE checklist for cohort studies.

Participants

All patients with a physician confirmed intermittent claudication who started community-based supervised exercise therapy were eligible for inclusion. The diagnosis of intermittent claudication was confirmed with an ankle-brachial index (ABI) <0.9 at rest. Exclusion criteria were the absence of a baseline measurement, less than one valid initial claudication distance measurement and initial claudication distance of 1600 meters or more at baseline [12]. A cut-off value for all initial claudication distances was set at

1600m. For practical reasons incline and testing duration in standard practice are maximized to 30 minutes (1600m).

Variables

The primary outcome measurement was initial claudication distance at 1, 3, 6 or 12 months of SET. In recent years, there has been an increased focus on patient-centered care, defined by the Institute of Medicine (IOM) as 'providing care that is respectful of and responsive to individual patient preferences, needs, and values, and ensuring that patient values guide all clinical decisions' [13]. The hindrance of patients with intermittent claudication is that they are limited by pain while walking. During physiotherapy treatment patients are instructed to walk as far as they can through the pain (absolute claudication distance), until claudication pain becomes so severe that the patient is forced to stop [4]. However, the absolute claudication distance does not correspond with the distance a patient would walk in the course of daily activities as few will by choice walk until their maximum pain threshold. To acknowledge the importance of the patients' wish to walk longer distances pain-free this study focuses on initial claudication distance as primary outcome to reveal determinants of walking distance in standard physiotherapy care. Independent variables include age, gender and the physiotherapy practice. Besides, body-mass index of each patient was calculated as weight (kg)/height squared (m^2) according to the clinical guideline on the Identification, Evaluation and Treatment of Overweight and Obesity in Adults [14]. Smoking behaviour was recorded as non-smoker, previous smoker and current smoker. Presence or absence of orthopaedic-, neurologic-, cardiac-, pulmonic- and internal comorbidity was registered according to the standard hospital registration. Besides, the presence or absence of vascular comorbidity was registered in the same way. As patients with intermittent claudication already suffer from a vascular disease in the category vascular comorbidity solely the presence or absence of Percutaneous Transluminal Angioplasty (PTA), recanalization, bypass operation, endarterectomy, hypertension, arrhythmia, cardiac decompensation and heart valve suffering was recorded. Detailed information about specific diseases that belong to the other mentioned five categories of comorbidity is reported in Appendix 1. Patient-related variables and comorbidity were evaluated at baseline.

Data source

Data for this cohort study was derived from prospectively collected data filled in by physiotherapists in electronic medical records as part of standard care. This registration tool was commissioned by the centre of evidence-based physiotherapy (www.cebp.nl) and realised by Convenience-Fastguide® (www.fastguide.eu). All patients provided their informed consent to register and use their medical data.

Supervised Exercise Therapy

All patients received supervised exercise therapy according to the evidence-based intermittent claudication guideline of the Royal Dutch Society for Physiotherapy [12] as part of usual care. A standardised graded treadmill test with a constant speed of 3.2 km/h according to Gardner et al. [15] was used as measure of initial claudication distance. The incline starts at 0% and is increased by 2% every two minutes. The initial claudication distance was evaluated by the physiotherapist at baseline and after 1, 3, 6 and 12 months of follow-up. All measurements were registered in the electronic medical record by the physiotherapist. Detailed information on the community-based exercise program has previously been published by our research group [16, 17].

Statistical methods

Data was analysed with a three-level mixed linear regression analysis. The three levels were physiotherapist, patients within therapists, and measurements within patients. Time and patient characteristics (gender, age, smoking status, body-mass index, comorbidity) were included as fixed effects. The continuous predictors age and body-mass index were centred by subtracting from age 68 years (median age in the sample) and from body-mass index 25 kg/m^2 (clinical cut-off for overweight; close to median 26 in sample), to allow interpretation of time effects on the outcome if there is interaction of age or body-mass index with time [18]. All categorical predictors were entered through dummy indicator coding, with as reference categories respectively baseline for time, non-smoker for smoking status, male for gender, and absence of disease for each comorbidity. Interactions of time with each patient characteristic were included in the model. Finally, outcome differences between therapists were included as a random intercept, and outcome differences between patients (as far as unexplained by the predictors) were accommodated by allowing for an unstructured covariance pattern of the repeated measures. The model was subsequently simplified by excluding non-significant interaction effects ($\alpha \geq .05$) from the model one-by-one. All available measurements of all patients were analysed without imputation for missing measurements, which is valid under the same assumptions as multiple imputation, and under less restrictive assumptions than complete cases analysis or simple imputation methods [18]. Values of all repeated measures in maximum pain-free walking distance after the first occurrence of the cut-off value initial claudication distance=1600m were reset to missing because of a maximized incline and testing duration of 30 minutes (1600m) in standard physiotherapy practice. Outcome measures were checked for normality. Predictors were checked for outliers (summary descriptive statistics and histograms) and multicollinearity by inspecting their Variance Inflation Factor (VIF) [19]. No VIFs above 10 were found, indicating absence of multicollinearity [20]. Further, in view of the skewed distribution of the outcome, two additional analyses to check the robustness of

the results were performed. First, body-mass index was left out of the analysis (30% missing values), leading to the inclusion of 1254 more patients into the analysis. Third and last, the outcome was dichotomized as 1 if initial claudication distance = 1600m and as 0 if initial claudication distance < 1600m, and was analysed with mixed logistic regression using the same modelling procedure as in the mixed linear regression of the continuous initial claudication distance measure. The results of the additional analyses were compared with the first analysis. In view of multiple testing, significant results are presented at the 1% and the 5% significance level, and results significant at the 5% level but not at the 1% level must be treated as tentative pending replication.

RESULTS

Descriptive data of participants

The inclusion criteria were met by 2995 patients. The average age of patients was 67 years. Comorbidities that were present in more than half of all patients were vascular comorbidity (62%), internal comorbidity (54%) and cardiac comorbidity (49%). Mean initial claudication distance at baseline was 270m and after 12 months of supervised exercise therapy 667m. The characteristics of the study population are described in Table 1.

The results of the three-level mixed linear regression analysis showed at a 1% significance level that being female (p=0.000), advanced age (p=0.000) and a high body-mass index (p=0.000) lead to less improvement in initial claudication distance after supervised exercise therapy. Cardiac comorbidity seemed to be associated with less improvement in initial claudication distance at a 5% level (p=0.011). In addition, all three interaction terms, time by age (p=0.000), time by vascular comorbidity (p=0.023) and time by body-mass index (p=0.023) were significantly associated with less initial claudication distance progress (Table 2). Interactions gender*time and smoking*time were tested but were not significant.

Table 1. Characteristics of the study population

Characteristic[a]	Total population *N*=2995[b]	Males *N*=1864	Females *N*=1131
Age, years	67.4 ± 9.9	67.0 ± 9.5	68.2 ± 10.4
BMI, kg/m^2	26.8 ± 4.3	26.8 ± 4.0	26.6 ± 4.7
Current smokers	1140 (41.5)	708 (41.5)	432 (41.5)
Orthopaedic comorbidity	570 (23.8)	325 (21.9)	245 (26.9)
Neurological comorbidity	555 (23.6)	353 (24.2)	202 (22.6)
Cardiac comorbidity	1163 (48.7)	756 (50.8)	407 (45.2)
Vascular comorbidity	1474 (61.6)	909 (61.0)	565 (62.5)
Pulmonary comorbidity	408 (17.9)	270 (19.1)	138 (16.0)
Internal comorbidity	1242 (54.4)	755 (53.2)	487 (56.4)
Baseline ICD, meter	269.6 ± 227.3	286.1 ± 235.8	242.8 ± 210.1
1 months ICD, meter	433.6 ± 333.4	456.4 ± 348.7	394.5 ± 301.5
3 months ICD, meter	531.9 ± 380.9	554.5 ±394.4	496.0 ± 355.6
6 months ICD, meter	605.3 ± 411.6	632.9 ± 420.0	562.8 ± 394.9
12 months ICD, meter	667.1 ± 446.1	672.8 ±448.1	658.2 ± 443.3

BMI: Body-Mass Index; ICD= Initial Claudication Distance

[a]Dichotomous variables are presented as N (%) and continuous variables as mean ± standard deviation; initial claudication distance is reported as median ± standard deviation.

[b]*N*=2995 is the maximum amount of patients that were included in one of our analysis.

For females the predicted initial claudication distance is 41m less than for males after 12 months of supervised exercise therapy. For patients with a cardiac comorbidity, the predicted initial claudication distance is 30m less after 12 months compared to patients without a cardiac comorbidity. Both interpretations apply when all other variables are kept constant.

To calculate the improvement in initial claudication distance from baseline to initial claudication distance at 1, 3, 6 and 12 months for the interactions with time the following regression equation was used:

Change in $ICD_{1,3,6,12months}$= B1*t(1,3,6,12)dum + b2*time*age(centered) + b3*time* BMI(centered)+ b4*time*vascularcomorbidity.

In general terms, per year increase in age (range 33-93) initial claudication distance improvement is 8 meters less after 12 months. Per unit increase of body-mass index (range: 16-46) the improvement of initial claudication distance is 10 meters less after 12 months and the presence of vascular comorbidity leads to 85 meters less improvement after 12 months of SET. In all three scenarios all other variables are hold constant (Fig-

ures 1-3 in Appendix 2 provide plots of predicted values for the total sample per subgroup of age, BMI and vascular comorbidity to visualize interactions with time).

Table 2. Final mixed linear model

Fixed- effects [*N*=1741]	Estimate	SE	t-value	p-value	95% Confidence Interval	
					Lower	Upper
Intercept	315.48	22.869	13.80	0.000	270.59	360.37
Gender	-40.72	11.613	-3.51	0.000	-63.50	-17.94
Age[a]	-4.06	0.601	-6.75	0.000	-5.24	-2.88
BMI[a]	-4.68	1.338	-3.50	0.000	-7.30	-2.06
Past smoker[b]	19.06	19.109	1.00	0.319	-18.43	56.54
Current smoker[b]	-34.27	19.930	-1.72	0.086	-73.36	4.82
Orthopaedic comorbidity	5.32	13.585	0.39	0.695	-21.32	31.97
Neurological comorbidity	-4.17	13.483	-0.31	0.757	-30.61	22.27
Cardiac comorbidity	-29.55	11.549	-2.56	0.011	-52.20	-6.90
Vascular comorbidity	-11.00	11.288	-0.98	0.330	-33.15	11.14
Pulmonary comorbidity	-17.94	14.875	-1.21	0.228	-47.12	11.24
Internal comorbidity	-9.14	11.708	-0.78	0.435	-32.11	13.82
Time 1 dummy	165.95	7.527	22.05	0.000	151.19	180.71
Time 3 dummy	305.16	11.238	27.15	0.000	283.12	327.21
Time 6 dummy	439.01	18.214	24.10	0.000	403.27	474.75
Time 12 dummy	584.84	29.593	19.76	0.000	526.72	642.97
Age*time	-0.63	0.158	-3.98	0.000	-0.94	-0.32
BMI*time	-0.82	0.359	-2.28	0.023	-1.52	-0.11
Vascular comorbidity*time	-7.07	3.102	-2.28	0.023	-13.17	-0.98

Dependent Variable: ICD= Initial Claudication Distance.
BMI: Body-Mass Index; SE: Standard Error

To check the robustness of our findings two additional analysis were performed. First, we eliminated body-mass index from the model (30% missing values), resulting in 1254 more patients in the analysis. The results of this analysis were in agreement with the results of the mixed linear model described in table 2. Second, in view of non-normality of initial claudication distance the analysis was repeated by using a mixed logistic regression model after dichotomizing initial claudication distance as 1 if initial claudication distance = 1600m and as 0 if initial claudication distance <1600m. In accordance with the linear analysis, the results showed that being female (p=0.000), advanced age (p=0.000) and a high body-mass index (p=0.000) were associated with shorter initial claudication distance at all-time points. Furthermore, for current smoking (p=0.031) and vascular comorbidity there seemed to be a negative association with initial claudication distance (p=0.006). None of the interaction terms were significant, probably due to loss of power by dichotomization.

DISCUSSION

This study showed that female gender, advanced age, a high BMI and cardiac comorbidity are associated with less improvement in initial claudication distance after 1, 3, 6 and 12 months of supervised exercise therapy. In addition, the interaction time by age, time by body-mass index and time by vascular comorbidity were significantly associated with initial claudication distance. Additional analysis showed that there might be a negative association between vascular comorbidity and initial claudication distance and well as between cigarette smoking and initial claudication distance.

Some limitations are worth noting. First, due to the cross-sectional design of this study no causality can be inferred. Second, the absence of a control group and a randomisation procedure prevents interpretation of time effects as treatment effects. Time effects may also have been detected due to spontaneous recovery or treatments patients follow or experience outside the physiotherapy setting. Third, comorbidity was registered at the first visit, hence before the start of supervised exercise therapy. Therefore, it was not possible to investigate whether the presence of comorbid diseases changed over time. Fourth, the exact training program for each individual patient was not recorded. In general, the recommendations stated in the guideline intermittent claudication of the Royal Dutch Society for Physiotherapy are used to treat patients with peripheral arterial disease. However, we have no information about whether the general recommendation was adjusted for an individual patient. Therefore, the influence of variance in treatment on initial claudication distance after supervised exercise therapy could not be investigated.

Noteworthy is the fact that this study highlights a significant association with initial claudication distance for age, gender, body-mass index, and cardiovascular comorbidity at one go. When looking at previous research, the hampering association of all these factors already has been established [5-10]. However, it was spread throughout different studies, each presenting the adverse effect of one or two patient characteristics and/or comorbidity on walking distance in patients with intermittent claudication. A possible explanation might be that the sample sizes of previous studies were relatively small (maximum *N*=460 [7]) in comparison with our study (*N*=2995). Furthermore, for this study patients were not intentionally recruited, but data from electronic medical records was used, which allowed the research team to investigate which patient characteristics and comorbidity affect initial claudication distance in the standard physiotherapy care setting.

The inverse association between anthropometric indices like gender, age and body-mass index and walking distance has been previously studied. To illustrate, Troosters et al. [21] highlighted that 66% of the variability in walking distance assessed by the six-

minute walk test in healthy participants aged 50-85 years is attributable to age, gender and body-mass index.

Applying these finding to patients with intermittent claudication, a systematic review of Robeer et al. [22] showed that older patients respond less favourably to supervised exercise therapy compared to their younger counterparts. Changes in the cardiovascular system that occur with aging might explain why advanced age reduces the improvement in initial claudication distance after supervised exercise therapy. Alterations in cardiovascular physiology like a reduction in a heart's peak capacity to pump blood by 5% to 10% per decade might cause a diminished aerobic capacity with increasing age. Furthermore, with advanced age, the elasticity of arteries decreases and vascular walls thicken. This results in a slower exchange between oxygen and waste products [23]. As intermittent claudication is already associated with a decreased blood flow to the lower extremities particular during times of increased metabolic demand such as during supervised exercise therapy, above mentioned age-related cardiovascular adaptations might worsen muscle oxygen supply. Thus, the combination of peripheral arterial disease and age-related cardiovascular adaptations might cause oxygen ischemia faster; the muscle may not receive as much oxygen as needed to support physical activity and this might explain why initial claudication distance is lower in older patients with intermittent claudication compared to their younger counterparts. The capacity to perform aerobic exercise also depends on the ability of the heart to augment its output to the exercising muscles. This ability is often impaired in patients with cardiac comorbidity. Results of the present study demonstrate that patients with cardiac comorbidity show fewer improvements in initial claudication distance after supervised exercise therapy, which might be caused by inadequate blood flow to the active skeletal muscle secondary to impaired cardiac output. Research has shown that patients with cardiac diseases may achieve less than 50% of the maximum cardiac output attained by individuals without cardiac disease [24].

Regarding the inverse association between a high body-mass index and less improvement in initial claudication distance after supervised exercise therapy, previous research reported that body-mass index is a predictor of walking ability and functional capacity. Overall, it seems that increased body mass, either around the hip and thighs (gynoid obesity) or around the belly (android obesity) reduces walking ability and has a negative impact on functional capacity. The results of studies whether high fat mass or low lean mass are more important in the association between obesity and walking capacity remain contradictory. A study by Jankowski et al. [25] and a study by Davison et al. [26] found that a higher fat-mass is more important than low lean mass in the association with mobility-related disability. In contrast, a study of Newman et al. [24] showed an independent effect of low lean mass on walking ability.

The results of the present study also report that females show less improvement in initial claudication distance compared to males. Microvascular gender differences in

patients with intermittent claudication have been previously reported and might explain the differential improvement in initial claudication distance between men and women [27, 28]. A lower haemoglobin oxygen saturation of the calf muscles combined with a more impaired microvascular function seems to cause greater muscle ischemia during supervised exercise therapy in women compared to men [27, 28]. Other general gender-based biochemical differences like higher levels of oxidative stress and inflammation that are common in postmenopausal women might also contribute to lower improvements in initial claudication distance [27]. Nevertheless, other differences such as motivation, willingness to walk through claudication pain and pain tolerance threshold might be additional explanatory factors.

To check the robustness of our findings among others mixed logistic regression analysis was performed. This analysis was the only supplementary analysis reporting that addionally current smoking and vascular comorbidity seemed to be associated with less improvement in initial claudication distance after supervised exercise therapy. Nevertheless, previous research reported that current smoking is associated with poorer measures of exercise capacity during treadmill testing, including lower peak oxygen update and earlier onset of claudication pain during walking. A study of Afaq et al. [29] found that current smokers have significantly lower rates of tissue oxygenation at peak claudication distance, which might explain the lower initial claudication distance improvements in current smokers compared to non- or past-smokers found in this additional analysis. Peripheral factors that impact walking ability and therefore might explain lower initial claudication distance due to vascular comorbidity may include abnormalities in the endothelial function like vasodilatory capacity during physical activity and distribution of cardiac output. Since only one of the additional analysis showed current smoking and vascular comorbidity being predictors of initial claudication distance, these two findings should be interpreted with caution. Due to dichotomization of the outcome variable we lost power in the analysis, which might also explain why none of the interaction terms was significant.

In conclusion, the present study showed that being female, advanced age, high body-mass index and cardiac comorbidity are associated with less improvement in initial claudication distance after supervised exercise therapy. Because this large prospective usual care cohort study showed that the association of all these factors remained in place, subgroups of patients who benefit less from supervised exercise therapy have been most certainly identified. Taking care of these patients who benefit less from supervised exercise therapy is a crucial preparatory step to be able to early adjust treatment expectations and treatment programme.

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APPENDIX

APPENDIX 1. COMORBIDITY

Orthopaedic disease was considered to be present in patients with one of the following conditions: arthritis, rheumatoid arthritis, polyarthritis, osteoporosis, joint prosthesis, arthrogenic impairment, congenital dysplasia, congenital scoliosis, M. Scheuerman, M. Bechterew, fractures, hyperplasia / malignancy, Reiter's syndrome, Systemic Lupus Erythematous (SLE), psoriasis, polymyositis and other orthopedic disorders. Patients with a cerebrovascular accident / a transient ischaemic attack / central paresis, peripheral nerve disease, cerebellar disorders / encephalopathy, multiple sclerosis / amyotrophic lateral sclerosis / spinal cachexia, Parkinson / Extrapyramidal disorders, hernia nuclei pulposi with motor loss, radiculopathy / radicular syndrome, Paraplegics (traumatic / partial), neurotrauma, hyperplasia / malignancy or other **neurological disorders** in their medical history were considered to have neurological disease. **Cardiac disease** was viewed as the presence of at least one of the following: hypertension, abnormal electrocardiography, abnormal sinus rhythm, abnormal functional capacity, angina pectoris, heart failure, myocardial infarction, coronary arterial bypass graft, percutaneous transluminal coronary angioplasty, rhythm disorders, cardiac decompensation, heart valve suffering and other cardiac pathologies. **Vascular disease** was denoted to be present in patients with one of the following conditions in their medical history: PTA, recanalization, bypass operation, endarterectomy, hypertension, arrhythmia, cardiac decompensation, heart valve suffering and other vascular pathologies. **Pulmonic disease** was defined as the presence of at least one of the following: asthma, interstitial lung disease, diffuse interstitial lung disease / sarcoidosis, emphysema, cystic fibrosis, sleep apnea, hyperplasia / malignancy, chronic obstructive pulmonary disease and other pulmonic disorders. Patients with hypercholesterolemia, hyperlipidemia, elevated homocysteine levels, abnormal lipid spectrum, renal impairment, obesity, hyperplasia / malignancy, immunity disorder, diabetes mellitus and other internal pathologies in their medical history were esteemed to have **internal disease**.

APPENDIX 2. PLOTS OF PREDITED VALUES

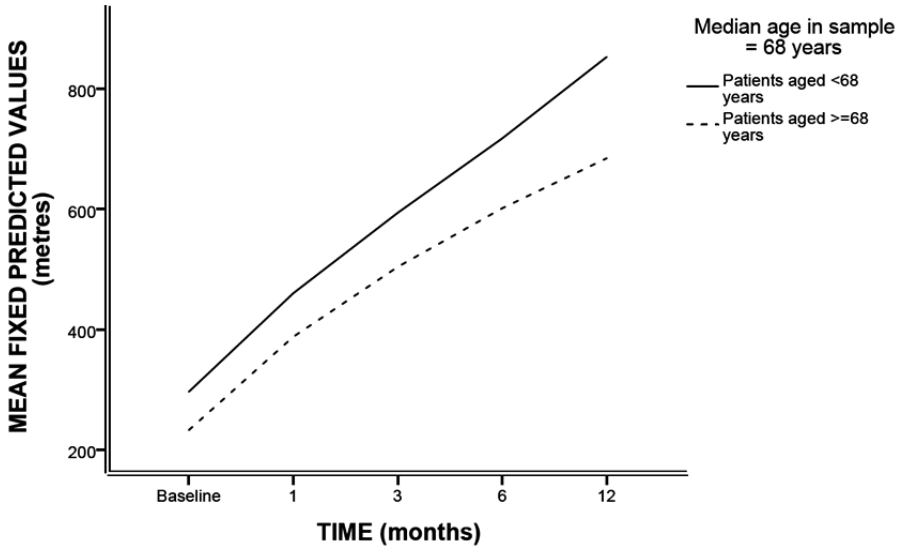

Figure 1. Plot of predicted values for the total sample per subgroup of age.
Change = B1 + B2*time*agecentered if vascular comorbidity absent and BMI = 25.

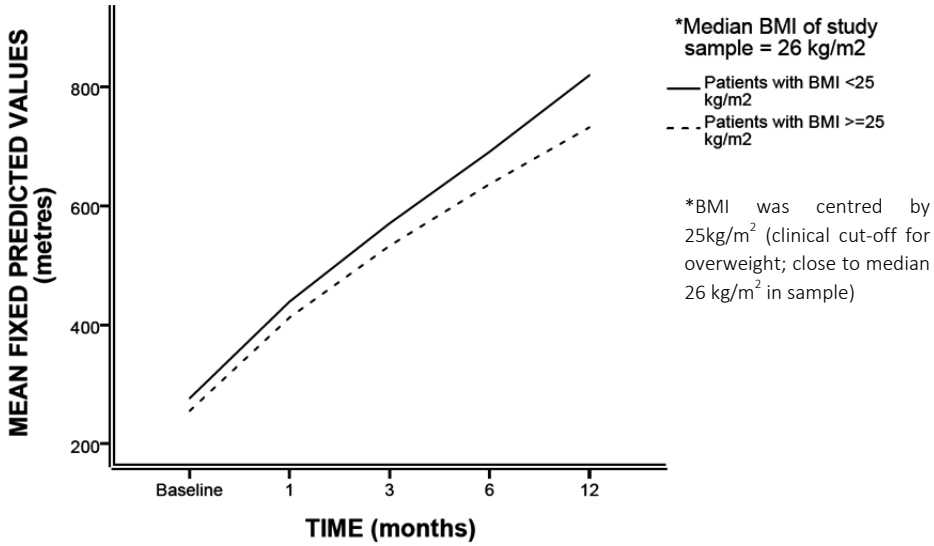

Figure 2. Plot of predicted values for the total sample per subgroup of BMI.
Change = B1 + B3*time*BMIcentered if age = 68 and vascular comorbidity absent.

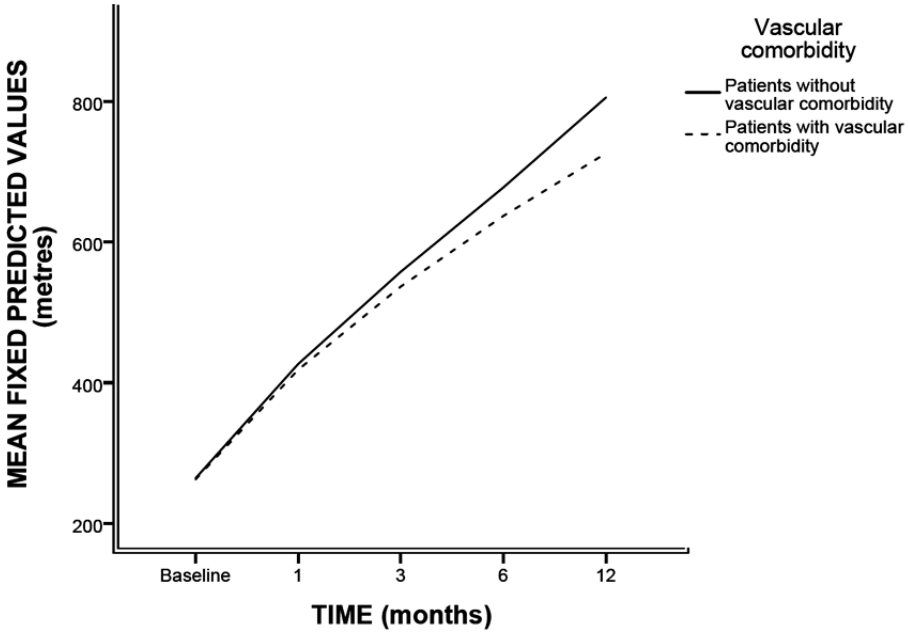

Figure 3. Plot of predicted values for the total sample per subgroup of vascular comorbidity. Change = B1 + B4*time*vascular comorbidity if age = 68 and BMI = 25.

Chapter 5

How well do Randomized Controlled Trials Reflect Standard Care:

a Comparison between Scientific Research Data and Standard Care Data in Patients with Intermittent Claudication

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ABSTRACT

Objective:

The aim of the present study was to assess the degree and impact of patient selection in randomized controlled trials by describing commonly used exclusion criteria, and by comparing baseline characteristics and treatment responses of patients included in clinical trials and patients treated in standard care.

Methods:

We compared data from randomized controlled trials with unselected standard care data. First, we systematically reviewed randomized controlled trials that investigated the effect of supervised exercise therapy in patients with intermittent claudication. For each of the randomized controlled trials, we extracted and categorized the eligibility criteria and their justifications. To assess whether people in randomized controlled trials (n=1,440) differed from patients treated in daily practice (n=3,513), in terms of demographics, comorbidity and walking capacity, we assessed between group-differences using t-tests. To assess differences in treatment response, we compared walking distances at three and six months between groups using t-tests. Differences of ≥15% were set as a marker for a clinically relevant difference.

Results:

All 20 included randomized controlled trials excluded large segments of patients with intermittent claudication. One-third of the randomized controlled trials eligibility criteria were justified. Despite, the numerous eligibility criteria, we found that baseline characteristics were largely comparable. A statistically significant and (borderline) clinically relevant difference in treatment response after three and six months between trial participants and standard care patients was found. Improvements in maximum walking distance after three and six months were significantly and clinically less in trial participants.

Conclusions:

The finding that baseline characteristics of patients included in randomized controlled trials and patients treated in standard care were comparable, may indicate that randomized controlled trial eligibility criteria are used implicitly by professionals when referring patients to standard physiotherapy care. The larger treatment response reported in standard physiotherapy care compared to clinical trials, might suggest that scientific studies underestimate the benefits of supervised exercise therapy in patients with intermittent claudication.

INTRODUCTION

"Can I translate results found in patients enrolled in a randomized controlled trial to the patient I am treating in my daily clinical practice?" This is one of the fundamental questions healthcare professionals have to ask themselves when interpreting scientific evidence. Concerns frequently arise as to how well a therapy may perform beyond highly selected patient populations and in different clinical settings than those studied in randomized controlled trials [1-5].

Differences between patients participating in randomized controlled trials and patients treated in standard care, as well as differences in clinical interventions between randomized controlled trials and standard care might affect the effectiveness of a therapy. Randomized controlled trials are only able to guide standard care and clinical decision-making when the research findings can be expected to be similar in other groups of patients not included [6, 7]. This requirement is not always met, which makes it difficult for clinicians to know to what extent the evidence for the effectiveness of an intervention applies to a given patient [8]. In this study, we aim to illustrate the degree of patient selection in randomized controlled trials by comparing baseline characteristics of patients included in clinical trials and patients treated in standard physiotherapy care. Furthermore, we aim to describe the differences in treatment response between patients enrolled in randomized controlled trials and those treated in standard care. Patients with intermittent claudication undergoing supervised exercise therapy are used as a case example, as our group has ample experience with both intermittent claudication and supervised exercise therapy (helping us to correctly interpret the utilized eligibility criteria) and access to a large, well-documented, unselected database of patients with intermittent claudication undergoing supervised exercise therapy (allowing a direct comparison between scientific research and real-life practice).

We aim to address the following three research questions:

1. Which patients with intermittent claudication are excluded in randomized controlled trials studying the effect of supervised exercise therapy and what are the reasons for excluding these patients?
2. To what extent are baseline characteristics of patients with intermittent claudication included in randomized controlled trials and patients with intermittent claudication treated with supervised exercise therapy in standard care comparable?
3. To what extent are supervised exercise therapy treatment responses (in terms of maximum walking distance) after three and six months of patients included in randomized controlled trials and patients treated in standard physiotherapy care comparable?

We hypothesized that, due to a strict selection of patients with intermittent claudication participating in randomized controlled trials (favouring less complex patients), the baseline maximum walking distance and the improvement in maximum walking distance after three and six months of supervised exercise therapy is larger in randomized controlled trials as compared to the treatment responses of patients with intermittent claudication treated in standard supervised exercise therapy care.

MATERIALS AND METHODS

Study design

We used the convergent parallel design [9] to compare two separate data sources: 1. data from randomized controlled trials investigating the effect of supervised exercise therapy in patients with intermittent claudication and 2. data from patients with intermittent claudication treated with supervised exercise therapy in the context of standard care physiotherapy. Both data sources were extracted and analyzed during the same phase of this study. Using qualitative data on the applied eligibility criteria and their justifications, we studied the extent of patient selection in randomized controlled trials. We extracted quantitative data of baseline characteristics and maximum walking distance from randomized controlled trials, and compared it with data from standard care physiotherapy to study differences at baseline and in treatment response after three and six months between patients included in randomized controlled trials and patients treated in standard care. Both qualitative and quantitative data were combined to formulate an overall interpretation of the results. To enhance transparency and reproducibility this article is written according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) [10].

Systematic review

Information sources and search

We performed a systematic search of articles from scientific medical journals published in the electronic online databases MEDLINE (PubMed), Embase (Ovid) and Cochrane Library up to mid-August 2015. The search strategy was developed by SD and TH and included MeSH terms and keywords and is presented in Appendix 1. To identify additional articles, all reference lists were checked for further relevant citations. We compared trials reporting information on the same set of patients and only included those with the most complete information on the patients' baseline characteristics and treatment response.

Study selection

Studies were eligible for inclusion if: 1. the design was an randomized controlled trial comparing supervised exercise therapy in patients with symptomatic peripheral arterial disease with standard care and/or other exercise recommendations. We focus on randomized controlled trials only, because they are accepted as the most unbiased measure of the efficacy of an intervention; 2. Peripheral arterial disease was diagnosed by the Ankle-Brachial Index (ABI) <0.9 in rest and/or <0.73 after exercise, because these are the criteria for patients to enter physiotherapy care; 3. the authors reported maximum walking distance or time measured by a graded treadmill test so that the outcome measure between randomized controlled trials and standard care is equivalent or can be recalculated to become equivalent [11]. All citations were independently screened and reviewed by SD and TH using the online software for intervention reviews Covidence supported by Cochrane [12]. We identified randomized controlled trials investigating the effect of supervised exercise therapy in patients with intermittent claudication on the basis of title and abstract. A more detailed inquiry based on full-text screening ensured that only articles fulfilling the eligibility criteria mentioned above were included in the meta-analysis.

Data collection process and data items

To evaluate eligibility criteria used and reasons for excluding specific patients, we listed first author, publication year and eligibility criteria per trial. In a second table, we recorded justifications for eligibility criteria applied per randomized controlled trial. Information on eligibility criteria and justifications for eligibility criteria used was extracted in duplicate by SD and TH.

To extract relevant data on baseline characteristics we used a self-designed, standardized data extraction form. Data about the author, the publication year, the country in which the randomized controlled trial was conducted, the mean age (years), the percentage of males, the mean body mass index (kg/m^2), the percentage of smokers and mean baseline maximum walking distance in meters of the supervised exercise therapy group was listed by TH and checked by SD. Only data from the supervised exercise therapy group of randomized controlled trials was used, because the aim of the present study is to compare research data with patients treated with supervised exercise therapy in standard care physiotherapy.

We extracted data on treatment outcome using a second self-designed standardized data sheet. Data extraction was done by SD and controlled by TH. We obtained exercise training and testing parameters (exercise type, exercise length, exercise duration, exercise frequency, walking speed, presence/absence of supervision and treadmill test protocol). In addition, we listed the number of patients that received supervised exercise therapy as well as mean maximum walking distance in meters after three and six

months. Maximum walking distance presented in time (minutes or miles per hour) as well as maximum walking distance recorded in feet was converted into meters [13, 14].

Risk of bias across studies

We assumed that summary statistics on treatment outcome, defined as maximum walking distance, were adequately reported in all 20 randomized controlled trials. A normal distribution of data was assumed to be present in trials reporting mean maximum walking distance and standard deviation (SD) and a skewed data distribution was supposed to be present in trials reporting median and Interquartile range (IQR). Because in a skewed distribution the mean is pulled in the direction of extreme scores (tail), inadequate use of the summary statistic mean in randomized controlled trials included may have introduced over-reporting of maximum walking distance in case of right skewed data and under-reporting of maximum walking distance in case of left skewed data.

Quality assessment

The Physiotherapy Evidence Database PEDro stores randomized controlled trials conducted in the field of physiotherapy research. This database is updated once a month. The methodological quality of all randomized controlled trials stored in the database is rated with the PEDro scale by the well-trained staff of the Centre for Evidence-Based Physiotherapy. Results of the assessment of the methodological quality of trials are also published in the PEDro database. To ensure the quality of ratings all raters underwent training; all randomized controlled trials are rated twice; a third rater resolved possible disagreements; informal and non-systematic checks of the quality of some ratings were performed; and the opportunity for PEDro users to dispute trial ratings is offered.

The PEDro scale is a checklist of 11 scored questions (yes or no) rating the methodological quality of randomized controlled trials. Criteria focus on the external validity (criterion 1), the internal validity (criterion 2–9) and the statistical information provided (criterion 10 and 11). A 'yes' is only awarded when a criterion is clearly satisfied. Each satisfied item contributes one point to the total PEDro score (0 to 10 points), except for item 1 which is the only item related to the external validity of the trial. The PEDro scale is based on a Delphi list developed by Verhagen et al. [15]. Results of previous research show that the PEDro scale is reliable for use in systematic reviews of physiotherapy randomized controlled trials [16]. We found information about the methodological quality of all randomized controlled trials included in the present study in PEDro, except for Mays et al. [17], a very recent randomized controlled trial. The methodological quality of this randomized controlled trial was rated in duplicate (by SD and TH) using the PEDro scale. No disagreements between both raters occurred.

Standard physiotherapy care data

We used data from patients with a physician-confirmed symptomatic peripheral arterial disease (ABI <0.9 at rest) who were treated with supervised exercise therapy in standard care physiotherapy between 2006 and 2011. Patient data were prospectively collected by 197 physiotherapists using Electronic Medical Records. We did not include data of patients without a baseline measurement in the present study, because one aim was to compare baseline characteristics of patients enrolled in trials with baseline characteristics of patients treated in standard care physiotherapy.

Data of patient characteristics recorded in the electronic medical record include information on age, gender, BMI, smoking behavior and comorbidity. The BMI of each patient was calculated according to the clinical guideline on the Identification, Evaluation and Treatment of Overweight and Obesity in adults [18]. Smoking behavior was recorded as current smoker or current non-smoker. The presence or absence of cardiovascular comorbidity, pulmonary comorbidity, internal comorbidity, orthopedic comorbidity and neurologic comorbidity was recorded according to the standard hospital registration. Diseases belonging to all categories of comorbidity are listed in Appendix 2. Patients were treated with supervised exercise therapy according to the evidence-based guideline intermittent claudication recommendation of the Royal Dutch Society for Physical Therapy [19]. The primary outcome measurement of the therapy was improvement in maximum walking distance. To measure maximum walking distance, physiotherapists performed a standardized graded treadmill test according to the treadmill test protocol described by Gardner et al [20]. All data was gathered in the context of standard care physiotherapy. The ethics committee/institutional review board 'Medisch Ethische Toetsingscommissie van Atrium Medisch Centrum, Orbis Medisch en Zorgconcern en Zuyd Hogeschool' approved at August, 19th 2013 the physiotherapy cohort study. Data was gathered in the context of standard care. All participants signed written informed consent for their clinical records to be used and patient records/information was anonymized and de-identified prior to analysis (METC number: 13-N-85).

Data analysis

Because inclusion and exclusion criteria are interchangeable by merely adding a ‘not’ to any given criterion, we studied both to receive a complete picture of the eligibility criteria applied. To evaluate which eligibility criteria were applied in the included RCTs, SD and TH first independently listed all eligibility criteria per randomized controlled trial. Subsequently, both researchers in consultation categorized each of the inclusion and exclusion criteria. The following categories were created: ‘patient characteristics’, ‘unstable medication use’, ‘comorbidity’, ‘walking capacity’ and ‘other criteria’. Both assessors independently counted the number of trials in which the criteria per category oc-

curred; counts and percentages were listed. Finally, both researchers checked whether and how often justifications for applied eligibility criteria were provided. With regard to comorbidity, the percentage of randomized controlled trial participants with comorbidity was noted per randomized controlled trial. Comorbidity reported in randomized controlled trials was often disease-specific. To be able to compare randomized controlled trial participants with standard care physiotherapy patients with regard to comorbidity, we categorized disease-specific comorbidities listed in the randomized controlled trials into the categories of comorbidity that were used in the standard physiotherapy care electronic medical record data, namely: cardiovascular, pulmonary, internal, orthopedic and neurologic comorbidity. The disease-specific comorbidity reporting in randomized controlled trials did not allow us to estimate the percentage of participants with comorbidity per category due to possible double-counts of participants. Therefore, we calculated a worst-case and a best case-scenario. In the worst-case scenario, disease-specific cases of comorbidity were added up per randomized controlled trial and per category. In the best-case scenario, the highest percentage comorbidity per category and randomized controlled trial was listed. We compared both scenarios with the percentage of comorbidity in standard care patients. For the sake of clear presentation in the text, the average percentage between worst-case and best-case scenario will be presented.

To compare baseline characteristics of patients included in randomized controlled trials and patients seen in standard physiotherapy care, we first pooled relevant baseline characteristics (age, sex, BMI, smoker (yes/no), and maximum walking distance) of all individual trials according to the methods described in the Cochrane Handbook [21]. Second, we tested whether the pooled estimates from the randomized controlled trials were significantly different from the estimates of the same baseline characteristics of the standard care physiotherapy cohort, using t-tests. In addition, we depicted mean maximum walking distance and their respective standard deviations (SDs) per study and for the cohort in a forest plot to allow visual comparison. To investigate whether treatment response after supervised exercise therapy differs between treatment in standard care and treatment in randomized controlled trials, we described the differences in maximum walking distance in meters after three and six months. Median maximum walking distance after three and six months of standard care was compared with pooled estimates of the treatment response measured in randomized controlled trials using a t-test. Furthermore, a difference in maximum walking distance between patients included in randomized controlled trials and patients treated in standard care of ≥15% was set as a marker for a clinically relevant difference [22]. We performed sensitivity analysis to take care of different treadmill protocols used to assess maximum walking distance in different randomized controlled trials.

RESULTS

Overall, randomized controlled trials provided data about 1,440 patients, and we used data of 3,531 patients from standard care physiotherapy. First, we present the results of our systematic review on randomized controlled trials investigating the effect of supervised exercise therapy in patients with intermittent claudication. Then, we show information about the eligibility criteria applied in randomized controlled trials and reasons for exclusion, followed by the results of our comparison of randomized controlled trial data and standard care data at baseline and after three and six months.

Study selection

The systematic search identified 16,551 potentially eligible articles in total, and 72 full-text randomized controlled trials were recognized for possible inclusion. During full-text screening, we excluded randomized controlled trials for the following reasons: a comparator other than any exercise recommendation or 'doing nothing' (12%); inappropriate patient group(s) (14%); maximum walking distance or walking time was not reported (14%); a nonrandomized design (6%); or supervised exercise therapy was not the intervention (35%). After identification of duplicate reports (21%), 20 eligible randomized controlled trials remained. A flow diagram of screened, eligible and included randomized controlled trials is presented in figure 1 [17, 23-41].

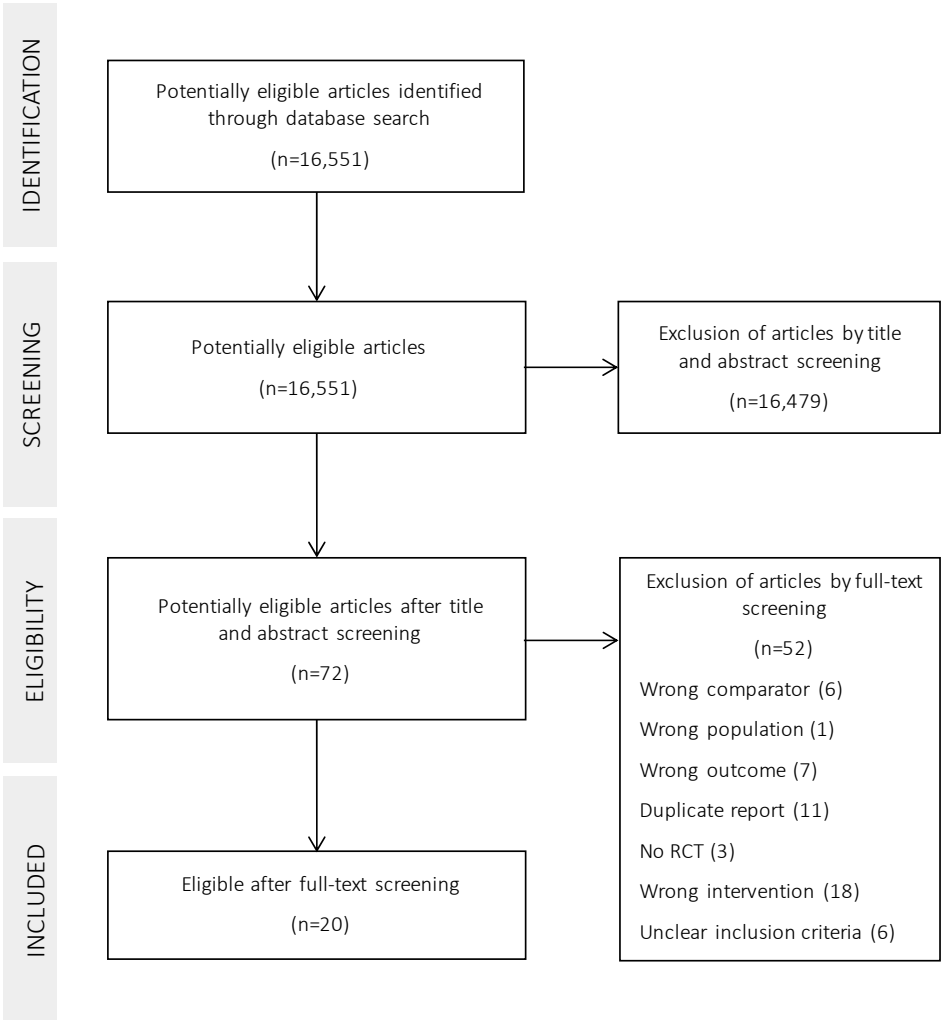

Figure 1. Flow diagram of screened, eligible and included randomized controlled trials.

Methodological quality

Total PEDro quality scores varied from 3 to 7 out of a maximum of 10 points. In all randomized controlled trials bias occurred due to a lack of blinding of subjects and therapists. In addition, 80% of the trials reported that group allocation was not concealed, 75% had no blinded assessors and 55% of all randomized controlled trials did not report information about an intention-to-treat analysis (Appendix 3).

Inventory of eligibility criteria and reasons for exclusion

Patient characteristics were the reason for exclusion in 30% of the randomized controlled trials (Table 1). Patients younger than 18 were excluded most often (20% of trials). (Unstable) lipid lowering, anti-platelet and antihypertensive medication use was the reason for exclusion in 65% of the trials. Patients were excluded due to the presence of comorbidity in all trials. Cardiovascular comorbidity (85%) and internal comorbidity (50%) were the main comorbidities for exclusion. Patients that suffer from a pulmonary and/or an orthopedic comorbidity were excluded in 40% of the trials. Impairment in walking capacity was the reason for exclusion in 70% of the randomized controlled trials. Being unable to walk on a treadmill with at least a speed of 3.2 km/h (35%) and gait abnormalities that had a different cause than peripheral arterial disease (45%) were most often reported. Other criteria were the reason for exclusion in 55% of the trials. Within this group, vascular surgery, angioplasty, lumbar sympathectomy and lower extremity revascularization in the six months preceding or scheduled at the start of the trial were the main reason for exclusion (70%) (Table 1).

Table 1. Summary of eligibility criteria used in all RCTs

Eligibility criteria	Number (%) of randomized controlled trials in which each eligibility criterion was applied
Patient characteristics	
Age	6 (30)
<18 year	4 (20)
>70 year	1 (5)
Sex Female	1 (5)
Women in menopausal status and those taking estrogen	1 (5)
BMI ≥ 30 kg/m^2	1 (5)
Unstable medication use	13 (65)
Comorbidity	20 (100)
Cardiovascular	17 (85)
Pulmonary	8 (40)
Internal	10 (50)
Orthopedic	8 (40)
Neurologic	5 (25)
Walking capacity	14 (70)
Unable to walk on a treadmill at a speed of at least 3.2 km/h	7 (35)
Gait abnormalities not due to peripheral arterial disease	9 (45)
Maximum walking distance >1600 meter at baseline	1 (5)
Maximum walking distance ≥ 500 meter at baseline	1 (5)
Maximum pain-free walking distance <150 meter	1 (5)

Eligibility criteria	Number (%) of randomized controlled trials in which each eligibility criterion was applied
No functional limitation due to intermittent claudication during treadmill test	3 (15)
Concurrent supervised exercise therapy	4 (20)
No native speaker	2 (10)
No insurance for supervised exercise therapy	1 (5)
Invasive peripheral arterial disease treatment (preceding 6 months or planned)	14 (70)
Substance abuse	1 (5)
Not living independently	2 (10)
Inability and/or unwillingness to exercise	4 (20)
Inability to obtain ABI	3 (15)
Rest leg pain	4 (20)
Unstable intermittent claudication symptoms (preceding 3 months)	1 (5)
Lifestyle not limited by intermittent claudication	2 (10)

Abbreviations: BMI = body mass index; ABI = Ankle Brachial Index

Regarding the presence of comorbidity, we found that cardiovascular comorbidity (65% vs 43%) and neurologic comorbidity (24% vs 12%) were more prevalent in standard care than in RCTs, respectively. Pulmonary (18% vs 16%), orthopedic (24% vs 20%) and internal comorbidity (54% vs 58%) were comparable between standard care and RCTs, respectively (Appendix 4).

Eligibility criteria were justified by authors in 30% of the randomized controlled trials [26, 29, 30, 33, 36, 37]. For instance, Gardner et al. [26] referred to the Guidelines of the American college of Sports Medicine [42] and a study conducted by Regensteiner et al. [43] for justification. The other five randomized controlled trials [26, 29, 33, 36, 37] reported detailed rationales for the applied eligibility criteria. Most frequent reasons for applied exclusion criteria were: (1) that the response to supervised exercise therapy might be affected by a certain characteristic; (2) that the aim of the study requires exclusion of certain groups of participants; (3) that patients with certain characteristics were not likely to complete supervised exercise therapy; (4) that the characteristic might limit and/or alter walking ability (see Appendix 5 for details).

Description and comparison of randomized controlled trial data and standard care data at baseline

A description of randomized controlled trial data and standard care data is displayed in Table 2. Supervised treadmill walking, coached by a physiotherapist or another exercise

specialist was the type of exercise in nearly all randomized controlled trials and in standard physiotherapy care. In trials supervised exercise therapy was performed on average for 22 weeks, three times a week with on average 42 minutes per exercise session. In standard physiotherapy care supervised exercise therapy was performed for on average 26 weeks, two to three times a week for 30 minutes per exercise session.
The mean (SD) age of patients with intermittent claudication included in the randomized controlled trials and patients with intermittent claudication that were referred to the physiotherapist for the treatment of supervised exercise therapy was 67 years, respectively. The percentage of males was significantly higher in the trial patients (73%) compared to the standard physiotherapy care patients (67%). The body mass index of patients treated in standard care was significantly higher in patients included in randomized controlled trials (26.7 kg/m^2 vs 26.0 kg/m^2, $p < 0.05$).

Mean baseline maximum walking distance was 382 m (range 116 to 805 m) in the 20 randomized controlled trials. In the standard supervised exercise therapy care population mean baseline maximum walking distance was 10 m less; this difference was not clinically relevant (3.14%) nor statistically significant ($p = 0.232$). Thirteen of the 20 randomized controlled trials reported higher mean maximum walking distance at baseline than in standard supervised exercise therapy care (Figure 2).

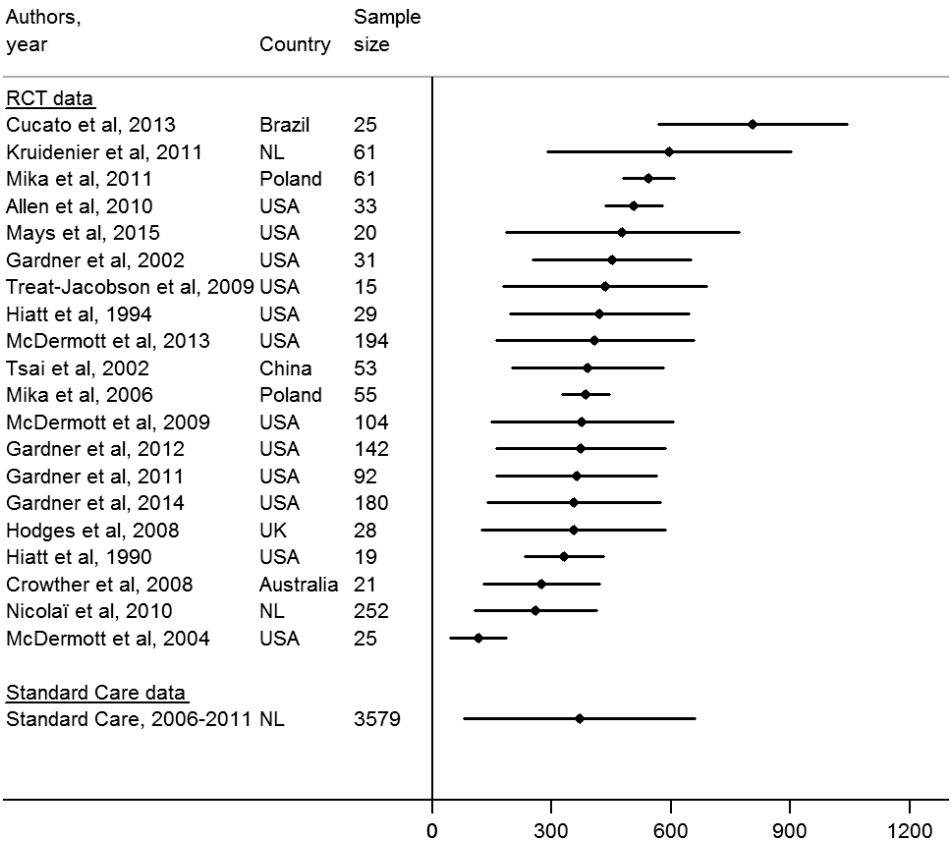

Figure 2. Forest plot illustrating the mean (SD) baseline maximum walking distance of patients included in the 20 randomized controlled trials and patients treated in standard supervised exercise therapy care.

Comparison of treatment response

Maximum walking distance after three months was studied in 65% and after six months in 35% of all randomized controlled trials. After three months maximum walking distance in randomized controlled trials was on average 605 m (range: 178 to 1100 m) and after six months 641 m (range: 610 to 956 m). After three and six months, improvement in maximum walking distance was greater in patients treated with supervised exercise therapy in standard physiotherapy care compared to patients included in randomized controlled trials (58 m more improvement after 3 months and 159 m more improvement after 6 months). After three and six months of supervised exercise therapy, the difference in improvement in maximum walking distance between patients included in randomized controlled trial and patients from standard care was statistically significant (both $p < 0.01$). A clinically relevant difference (≥15%) between patients included in randomized controlled trials and patients treated in standard care was only found after

six months of supervised exercise therapy (maximum walking distance improvement in patients treated in standard care was 25% higher). After three months of supervised exercise therapy the improvement in maximum walking distance was 14% higher in patients treated in standard physiotherapy care compared to patients included in randomized controlled trials and thus borderline clinically relevant (Table 2).

Sensitivity analysis

In some randomized controlled trials researchers used different treadmill protocols to assess maximum walking distance [44, 45] we found, however, that this did not result in differences in maximum walking distance assessed at baseline.

Table 2. Patient characteristics, parameters of exercise training, and maximum walking distance of randomized controlled trials (individually), randomized controlled trials (cumulatively) and standard care at baseline, 3 months and 6 months of supervised exercise therapy

	Baseline													3 months		6 months		
	Country	N	Age Mean (SD) (year)	Male (%)	BMI Mean (SD) (kg/m^2)	Smoker (% yes)	MWD Baseline Mean(SD) (meters)	Exercise type	Exercise Length (wk)	Exercise Duration (min)	Exercise Frequency (x per wk)	Walking speed (km/h)	Supervision (Yes/No)	N 3 mo	MWD 3 mo Mean(SD) (meters)	N 6 mo	MWD 6 mo Mean(SD) (meters)	MWD* test
Individual RCTs																		
Allen, 2010	USA	33	67 (12)	-	27.8 (5.0)	31	506 (71)	SET	14	40	3	3.2	Yes	15	680 (72)	-	-	GS
Crowther, 2008	Australia	21	69 (8)	48	28.8 (4.8)	19	274 (146)	SET	52	40	3	3.2	Yes	-	-	-	-	GS
Cucato, 2013	Brazil	25	63 (7)	100	25.6 (3.1)	24	805 (237)	SET	12	30	2	3.2	Yes	13	1100 (236)	-	-	GS
Gardner, 2002	USA	31	72 (4)	92	29.9 (4.3)	0	451 (199)	SET	76	40	3	3.2	Yes	-	-	17	809 (73)	GS
Gardner, 2011	USA	92	65 (11)	48	29.8 (6.0)	10	363 (201)	SET	12	45	3	3.2	Yes	33	481 (250)	-	-	GS
Gardner, 2012	USA	142	68 (8)	85	28.3 (4.7)	60	373 (212)	SET	26	40	3	3.2	Yes	-	-	80	664 (264)	GS
Gardner, 2014	USA	180	66 (10)	53	29.1 (6.2)	38	356 (218)	SET	12	40	3	3.2	Yes	60	487 (266)	-	-	GS
Hiatt, 1990	USA	19	60 (12)	100	-	58	331 (99)	SET	12	50	3	3.2	Yes	10	742 (187)	-	-	Hiatt
Hiatt, 1994	USA	29	67 (6)	100	-	70	421 (224)	SET	12	50	3	3.2	Yes	10	785 (390)	10	918 (390)	Hiatt
Hodges, 2008	UK	28	68 (8)	-	26.7 (3.4)	-	355 (230)	SET	12	30	2	3.2	Yes	14	623 (311)	-	-	GS
Kruidenier, 2011	NL	61	62 (10)	61	27.1 (4.2)	56	595 (307)	SET	26	30	2-3	3.2	Yes	32	974 (513)	34	956 (490)	GS

	Baseline													3 months		6 months		
	Country	N	Age Mean (SD) (year)	Male (%)	BMI Mean (SD) (kg/m^2)	Smoker (% yes)	MWD Baseline Mean(SD) (meters)	Exercise type	Exercise Length (wk)	Exercise Duration (min)	Exercise Frequency (x per wk)	Walking speed (km/h)	Supervision (Yes/No)	N 3 mo	MWD 3 mo Mean(SD) (meters)	N 6 mo	MWD 6 mo Mean(SD) (meters)	MWD* test
Mays, 2015	USA	20	65 (10)	80	28.5 (5.0)	-	478 (292)	SET	15	35	3	NR	Yes	-	-	-	-	GS
McDermott, 2004	USA	25	70 (9)	52	28.7 (5.3)	19	116 (70)	SET	14	50	3	3.2	Yes	17	178 (89)	-	-	GS
McDermott, 2009	USA	104	70 (11)	47	30.2 (6.7)	14	383 (227)	SET	26	40	3	3.2	Yes	-	-	48	619 (297)	GS
McDermott, 2013	USA	194	70 (10)	50	29.1 (6.7)	24	412 (248)	OGW	26	50	5	NR	No	-	-	86	504 (318)	GS
Mika, 2006	Poland	55	59 (8)	87	-	76	386 (59)	SET	14	50	3	3.2	Yes	27	584 (70)	-	-	Hiatt
Mika, 2011	Poland	61	63 (7)	87	27.7 (3.2)	80	543 (65)	SET	12	55	3	3.2	Yes	30	849 (61)	-	-	GS
Nicolaï, 2010	NL	252	66 (9)	63	27.9 (4.6)	42	260 (153)	SET	52	30	3	3.2	Yes	169	530 (573)	169	610 (692)	GS
Treat-Jacobson, 2009	USA	15	67 (10)	74	27.5 (4.3)	-	432 (255)	SET	12	60	3	3.2	Yes	-	-	-	-	Other
Tsai, 2002	China	53	76 (4)	83	23.3 (2.5)	-	389 (191)	SET	12	30	3	3.2	Yes	27	668 (198)	-	-	GS
Pooled estimates of RCTs	**World**	**1,440**	**67 (9)**	**73**	**26.0 (5.0)**	**39**	**382 (203)**	**SET**	**22**	**42**	**3**	**3.2**	**Yes**	**457**	**605 (407)**	**444**	**641 (495)**	**-**
Standard care	**NL**	**3,531**	**67 (10)**	**62***	**26.7* (4.3)**	**41**	**370 (287)**	**SET**	**26**	**30**	**2-3**	**3.2**	**Yes**	**1,738**	**690* (448)**	**1,252**	**800* (457)**	**GS**

Legend: *p < 0.05; Abbreviations: BMI = Body-Mass Index, MWD = Maximum Walking Distance, SD = Standard Deviation, SET = Supervised Exercise Therapy, OWG = Over Ground Walking, GS = Gardner- Skinner protocol, NR = Not reported; *detailed information about treadmill testing assessment can be found in Appendix 6.

DISCUSSION

All randomized controlled trials included in the present study excluded moderate to large segments of the population of patients with intermittent claudication, and the exclusion criteria applied were justified in only a third of the trials. It seems that most of the exclusion criteria are also implicitly used in standard physiotherapy care, because baseline characteristics of patients included in randomized controlled trials and patients treated in standard physiotherapy care were comparable. However, a statistically significant and (borderline) clinically relevant difference in the improvement in maximum walking distance after three and six months was found. The difference between trial treatment response and standard physiotherapy care treatment response suggests an underestimation of the benefits of supervised exercise therapy for the standard physiotherapy care setting.

The strengths of our study include the rigorous literature search, the data extraction check and the availability of a large real-life standard care supervised exercise therapy data registry. There are also some limitations. First, we did not have data on the exclusion criteria used in standard physiotherapy care, making a head-on comparison impossible. Second, due to a lack of disease-specific reporting of comorbidity in the standard care data, we could not compare patients included in trials exactly with patients treated in standard supervised exercise therapy care with regard to disease-specific comorbidity. Third, no information on possible supervised exercise therapy adaptations applied in standard physiotherapy care was available, nor did any of the randomized controlled trials provide treatment fidelity estimates. Finally, we had no control over how well standard supervised exercise therapy care data was recorded. Nevertheless, data on 3,531 patients was collected by 197 different physiotherapists and therefore we are inclined to accept that quality differences will balance out due to the large number of physiotherapists registering the data.

Our inventory of eligibility criteria and justifications for eligibility criteria used in randomized controlled trials investigating the effect of supervised exercise therapy in patients with intermittent claudication showed that all trials excluded large segments of the population of patients with intermittent claudication, yet this did not result in major differences at baseline. Patients were excluded due to comorbidity in all 20 randomized controlled trials. Cardiovascular comorbidity was the reason for exclusion in 85% of the randomized controlled trials and only one article justified this exclusion criteria, stating that cardiac symptoms might limit walking ability of patients with intermittent claudication to a greater extent than peripheral arterial disease [33]. Coronary artery disease was shown to be present in 46% to 58% of all patients with intermittent claudication [46, 47], which implies that the exclusion of patients with this comorbidity leaves half of patients with intermittent claudication with uncertainty and potential unintended harm

from generalizing trial results. Due to the fact that randomized controlled trials have limited financial resources, follow a strict intervention protocol and cardiac exercise testing would be recommended before the start of supervised exercise therapy, [11] the exclusion of patients with cardiovascular comorbidity seems understandable; however, this has the consequence of limiting the generalizability of the randomized controlled trials results. Patients who received invasive treatment in the preceding six months or were scheduled for an invasive intervention were also often excluded. McDermott et al. [33] excluded this patient group because lower extremity revascularization may alter walking ability. This justification is in line with previous research that has shown that invasive treatment is effective in increasing maximum walking distance at a follow-up to 12 months [48, 49]. Medication use (unstable and in general) as well as impairments in walking capacity were also reported as exclusion criteria in the majority of included randomized controlled trials, again with limited justification. A rationale for the eligibility criteria used is hardly ever provided, although international ethical guidelines for research involving human subjects [50, 51] and the CONSORT and the SPIRIT statement require justification of exclusion of study populations [52, 53]. Gardner et al. [26] did not explicitly report rationales for exclusion, but provided references [42, 43] as support for the exclusion criteria applied. However, these references are complex documents that keep the reader guessing about the exact reasons why patients have been deliberately excluded. The justification for exclusion criteria applied was made transparent on a more general level; hence explicit reporting is necessary to study concerns of unjustifiable exclusion of the study population. None of the 20 randomized controlled trials reported how many patients were excluded per eligibility criterion. Regardless, we also found that the majority of baseline characteristics of patients with intermittent claudication included in randomized controlled trials and patients with intermittent claudication treated in standard care were comparable (age, body-mass index, smoking behavior, comorbidity and maximum walking distance). We did observe a higher number of male patients in the randomized controlled trials, but we are unable to formulate a logical rationale for this difference. Our a-priori hypothesis that baseline maximum walking distance would be lower in standard supervised exercise therapy practice was thus rejected. This leads us to assume that patients with certain types of comorbidity are also not part of standard practice. There might be multiple underlying reasons. It could be that the impact of comorbidity on walking ability, exercise capacity, its severity or in general the presence of comorbidity discourages patients from seeking physiotherapy treatment. Previous research showed that comorbidity may require adaptations in physiotherapy as comorbidity negatively affects treatment outcomes of the index disease or as treatment for one disease may negatively interact with the treatment or natural course of the comorbidity [54]. It might also be that physiotherapists recognize additional risks of exercise training that emerge due to comorbidity and therefore advise against supervised exercise therapy [11]. Whatever the reason, we conclude that the degree of selection bias in randomized controlled trials on supervised

exercise therapy in people with intermittent claudication is minimal and would therefore likely reflect the general population of individuals with intermittent claudication.

Improvement in maximum walking distance after three and six months of supervised exercise therapy was significantly greater – both statistically as well as clinically – for patients treated in standard physiotherapy care compared to patients treated in randomized controlled trials, refuting our a-priori hypothesis. Considering that baseline maximum walking distance values were comparable, this difference might be attributed to differences in the utilized supervised exercise therapy treatment protocols. In general, patients in the randomized controlled trials and in standard care received supervised exercise therapy on a treadmill, three times a week at a walking speed of 3.2 km/h, except for the trial of McDermott et al. [35] where patients walked around an indoor track. Despite the fact that exercise duration per treatment session was on average 12 minutes longer in randomized controlled trials than in standard care, no striking differences between the description of supervised exercise therapy as applied in the randomized controlled trials and in standard care were found that explain this substantial disparity in treatment response; both largely follow the current recommendations for optimal supervised exercise therapy [55-57]. In our opinion, there are two possible explanations for the differences in treatment response: the therapeutic quality and fidelity of the provided interventions and differences in utilized methods. First, we expect that the therapeutic quality of the supervised exercise therapy interventions in standard practice is greater in comparison to supervised exercise therapy in randomized controlled trials. After all, specialized and well-trained therapists have considerable experience providing supervised exercise therapy to people with intermittent claudication, likely resulting in more personalized therapeutic interventions, as compared to the often rigid and highly standardized interventions provided in randomized controlled trials [58]. Following a highly standardized supervised exercise therapy protocol might cause the 'better patients' to be insufficiently challenged, while in standard care supervised exercise therapy treatment protocols might have been tailored to the individual patient circumstances in order to gain the maximum improvement in maximum walking distance. Moreover, trial participants may have been limited in their choice of possible co-interventions; after all, co-intervention is typically seen as a potential source of bias in randomized controlled trials. In contrast, patients with intermittent claudication who are referred to standard physiotherapy care for supervised exercise therapy will likely receive additional therapeutic recommendations, home-exercise programs and perhaps even treatment, which in turn could lead to a greater improvement in maximum walking distance over time.

Moreover, it is important to highlight that data from standard physiotherapy care was collected between 2006 and 2011 and supervised exercise therapy was back then in its infancy [59, 60]. Based on the positive effect of supervised exercise therapy, in 2011 a nationwide community based supervised exercise therapy network (ClaudicatioNet) was

initiated and launched in the Netherlands. The forefront of ClaudicatioNet is formed by specialised physical therapists providing high quality supervised exercise therapy, stimulating lifestyle changes and medication adherence [61, 62]. Due to the progress in quality of supervised exercise therapy care we speculate that repeating the present study with more recent standard care data might result in even a larger discrepancy between supervised exercise therapy effectiveness presented in randomized controlled trials and supervised exercise therapy applied in standard care.

Our assessment of the methodological quality of randomized controlled trials included showed that in all randomized controlled trials bias occurred because of lack of blinding and intention-to-treat analysis. Blinding is a critical methodological part of randomized controlled trials. However, the results of our quality assessment indicated that 100% of the included randomized controlled trials did not blind subjects and therapists and that the assessor was blinded in only a quarter of the studies. A number of studies previously reported a significant difference in the size of the estimated treatment effect between trials that reported blinding compared to those that did not (p=0.01), with an overall odds ratio 17% larger in studies that did not report 'double-blinding' [63-65]. Because none of the 20 included randomized controlled trials reported 'double-blinding', their estimated treatment effect represents an underestimation (-17%) of treatment effectiveness in ideal methodological circumstances. This means that our randomized controlled trial data is more comparable to the standard care data (no blinding), and that even despite the fact that the estimate of treatment effectiveness in randomized controlled trials is underestimated by 17% a statistical and (borderline) clinically relevant difference in treatment effectiveness has been detected after three and six months. Moreover, blinding of the outcome assessor is crucial to ensure unbiased ascertainment of treatment effectiveness [66]. However, the lack of blinding techniques that has been detected in the majority of randomized controlled trials included in the present study also enhances the comparability with our standard care data.

Less than half of all included randomized controlled trials performed an intention-to-treat analysis, which has been proven to be the least biased technique to estimate intervention effects in randomized controlled trials [67]. This is because an intention-to-treat analysis tests the hypothesis of a null effect of treatment in a statistically valid way, and if participants do not fully adhere to their assigned treatment an intention-to-treat analysis underestimates the treatment effect [68]. To maintain the benefits of randomization, intention-to-treat analysis requires the comparison to be based upon the treatment and control groups participants were randomly assigned to. In contrast, per-protocol analysis describes the outcomes of the participants who adhered to the research protocol, which can be useful to estimate the intervention's efficacy for those who actually received it. Nevertheless, this estimate is likely to be flawed (overestimated) due to nonadherence of participants [68]. Likewise, this also means that the treatment effect might be overestimated in 11 randomized controlled trials.

Methodological differences between the randomized controlled trial study design and our analysis of data from standard care physiotherapy must also be discussed. Overall, the main difference between our comparison of randomized controlled trials and observational standard care data is the fact that in the randomized controlled trials, supervised exercise therapy is randomly allocated to the patients, whereas in standard care patients are naturally exposed to supervised exercise therapy. In the latter, voluntarily going to the physiotherapist for supervised exercise therapy might be a characteristic of some patients and these patients might be different from those who do not voluntarily seek help by their physiotherapist for the treatment of intermittent claudication. It might be that patients with intermittent claudication who chose physiotherapy are healthier than patients with intermittent claudication that chose not to go to the physiotherapist. It might also be the case that the patients who receive supervised exercise therapy in the context of standard care have been chosen by someone else, such as the vascular surgeon who referred them to the physiotherapist for supervised exercise therapy. This possibly existing imbalance, which could also be called selection bias or referral bias, might have led to an overestimation of maximum walking distance improvement after supervised exercise therapy [69]. Furthermore, treatment compliance may not be equivalent between the randomized controlled trial and the standard care setting. The correctness of data entry in the electronic medical record might differ from the correctness of data entry from the randomized controlled trial, because standard care data is recorded within the workflow of daily practice and randomized controlled trials are often based on double-data entry and data checks. Although there are of course discrepancies between both settings that are the result of biological and methodological differences, a systematic review published in the New England Journal of Medicine concluded that observational studies did not systematically overestimate the magnitude outcomes as compared with results of randomized controlled trials [69].

CONCLUSION

All randomized controlled trials included in the present study excluded moderate- to large segments of the population of patients with intermittent claudication and exclusion criteria applied were justified in only one-third of the trials. Most of the exclusion criteria are also implicitly used in standard physiotherapy care and because of this baseline characteristics of patients included in randomized controlled trials and patients treated in standard physiotherapy care were comparable. However, a statistically significant and (borderline) clinically relevant difference in the improvement in maximum walking distance after three and six months was found. The difference between trial treatment response and standard physiotherapy care treatment response suggests an underestimation of the benefits of supervised exercise therapy for the standard physiotherapy care setting.

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APPENDIX

APPENDIX 1. SEARCH STRING AS UTILIZED IN PUBMED.

#1 Peripheral Arterial Disease [MeSH Terms] OR Arterial Occlusive Diseases [MeSH Terms] OR Intermittent Claudication [MeSH Terms]

#2 Peripheral Artery Disease [Text Word] OR Peripheral Artery Diseases [Text Word] OR Peripheral Arterial Disease [Text Word] OR Peripheral Arterial Diseases [Text Word] OR Arterial Occlusive Disease [Text Word] OR Artery Occlusive Disease [Text Word] OR Arterial Obstructive Disease [Text Word] OR Artery Obstructive Disease [Text Word] OR Intermittent Claudication [Text Word]

#3 Exercise [MeSH Terms] OR Exercise Therapy [MeSH Terms] OR Physical Therapy Modalities [MeSH Terms]

#4 exercise [Text Word] OR walk* [Text Word] OR treadmill [Text Word] OR physical training [Text Word]

#5 Search #1 OR #2

#6 Search #3 OR #4

#7 Search #5 AND #6

APPENDIX 2. CATEGORIES OF COMORBIDITY (COHORT DATA).

Cardiac comorbidity included the presence of:
Hypertension, abnormal electrocardiography, abnormal sinus rhythm, abnormal functional capacity, angina pectoris, heart failure, myocardial infarction, coronary arterial bypass graft, percutaneous transluminal coronary angioplasty, rhythm disorders, cardiac decompensation, heart valve suffering, PTA, recanalization, bypass operation, endarterectomy, hypertension, arrhythmia, cardiac decompensation, heart valve suffering and other cardiovascular pathologies.

Pulmonary comorbidity was defined as having:
Asthma, interstitial lung disease, diffuse interstitial lung disease / sarcoidosis, emphysema, cystic fibrosis, sleep apnea, hyperplasia / malignancy, chronic obstructive pulmonary disease and other pulmonic disorders.

Internal comorbidity involved:
Hypercholesterolemia, hyperlipidemia, elevated homocysteine levels, abnormal lipid spectrum, renal impairment, obesity, hyperplasia / malignancy, immunity disorder, diabetes mellitus and other internal pathologies.

Orthopedic comorbidity contained of:
Arthritis, rheumatoid arthritis, polyarthritis, osteoporosis, joint prosthesis, arthrogenic impairment, congenital dysplasia, congenital scoliosis, M. Scheuerman, M. Bechterew, fractures, hyperplasia / malignancy, Reiter's syndrome, Systemic Lupus Erythematous (SLE), psoriasis, polymyositis and other orthopedic disorders were described to have.

Neurologic comorbidity was present in patients with:
Cerebrovascular accident / a transient ischemic attack / central paresis, peripheral nerve disease, cerebellar disorders / encephalopathy, multiple sclerosis / amyotrophic lateral sclerosis / spinal cachexia, Parkinson / Extrapyramidal disorders, hernia nuclei pulposi with motor loss, radiculopathy / radicular syndrome, Paraplegics (traumatic / partial), neurotrauma and hyperplasia / malignancy.

APPENDIX 3. METHODOLOGICAL QUALITY OF RCTS.

Table 1. Methodological quality of all randomized controlled trials included.

	Eligibility criteria	Random allocation	Concealed allocation	Baseline comparability	Blind subjects	Blind therapists	Blind assessors	Adequate follow-up	Intention-to treat analysis	Between-group comparisons	Point estimates and variability	Total*
Allen et al, 2010	Yes	Yes	No	Yes	No	No	No	No	No	Yes	Yes	4/10
Crowther et al, 2008	Yes	Yes	No	Yes	No	No	No	Yes	No	Yes	Yes	5/10
Cucato et al, 2013	Yes	Yes	No	Yes	No	No	No	Yes	No	Yes	Yes	5/10
Gardner et al 2002	Yes	Yes	No	Yes	No	No	No	No	Yes	Yes	Yes	5/10
Gardner et al, 2011	Yes	Yes	Yes	Yes	No	No	No	No	No	Yes	Yes	5/10
Gardner et al, 2012	Yes	Yes	No	Yes	No	No	No	No	Yes	Yes	Yes	5/10
Gardner et al, 2014	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes	6/10
Hiatt et al, 1990	No	Yes	No	Yes	No	No	No	No	No	Yes	Yes	4/10
Hiatt et al, 1994	No	Yes	No	Yes	No	No	No	Yes	No	Yes	Yes	5/10
Hodges et al, 2008	Yes	Yes	No	No	No	No	No	No	No	Yes	Yes	3/10
Kruidenier et al, 2011	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	7/10

	Eligibility criteria	Random allocation	Concealed allocation	Baseline comparability	Blind subjects	Blind therapists	Blind assessors	Adequate follow-up	Intention-to treat analysis	Between-group comparisons	Point estimates and variability	Total*
Mays et al, 2015	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	7/10
McDermott et al, 2004	Yes	Yes	No	Yes	No	No	No	No	Yes	Yes	No	4/10
McDermott et al, 2009	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	7/10
McDermott et al, 2013	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	7/10
Mika et al, 2006	Yes	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes	6/10
Mika et al, 2011	Yes	Yes	No	Yes	No	No	Yes	Yes	No	No	Yes	5/10
Nicolaï et al, 2010	Yes	Yes	Yes	Yes	No	No	Yes	No	No	Yes	Yes	6/10
Treat-Jacobson et al, 2009	Yes	Yes	No	Yes	No	No	No	Yes	No	Yes	Yes	5/10
Tsai et al, 2002	Yes	Yes	No	Yes	No	No	No	No	Yes	Yes	Yes	5/10

APPENDIX 4. COMPARISON OF COMORBIDITY.

Table 1. Number of patients with a disease-specific comorbidity reported in randomized controlled trials and approximate estimate (worst and best case scenario) of the percentage patients included in randomized controlled trials with a comorbidity per category compared to the percentage patients with a comorbidity per category from standard physiotherapy care

		Allen 2010	Crowther 2008	Cucato 2013	Gardner 2011	Gardner 2012	Hiatt 1994	Kruidenier 2011	McDermott 2004	McDermott 2009	McDermott 2013	Nicolai 2010	Treat-Jacobson 2009	Total RCTs	Standard care[a]
	Total N	N=76	N=21	N=25	N=80	N=142	N=29	N=70	N=32	N=103	N=194	N=304	N=25	N=1,101	N=3,541
Cardio-	N CAD	14					9		5		30				1983/3541
vascular	N CHF	5						20			22	76	14		(= 56%)
	N High BP		7	21	70	91	14	49					16		
	N IHD		5						5						
	Worst case	19	12	21	70	91	23	69	10		52	76	30	473/998 (= 47%)	
	Best case	14	7	21	70	91	14	49	5		30	76	16	393/998 (= 39%)	
Pulmonary	N COPD						4	8	2		26	63			637/3541 (= 18%)
	Worst and best case						4	8	2		26	63		103/629 (= 16%)	
Internal	N DM		4	5	34	35		14	12	44	64	69	7		1912/3541 (= 54%)
	N Dyslip.			23	71	83	7						19		
	N MS				62	78									
	N Chol↑.							61							

		Allen 2010	Crowther 2008	Cucato 2013	Gardner 2011	Gardner 2012	Hiatt 1994	Kruidenier 2011	McDermott 2004	McDermott 2009	McDermott 2013	Nicolai 2010	Treat-Jacobson 2009	Total RCTs	Standard care[a]
	Total N	N=76	N=21	N=25	N=80	N=142	N=29	N=70	N=32	N=103	N=194	N=304	N=25	N=1,101	N=3,541
	N Cancer										31				
	Worst case		4	28	167	196	7	75	12	44	95	69	26	723/1025 (= 71%)	
	Best case		4	23	71	83	7	61	12	44	64	69	19	457/1025 (= 45%)	
Orthopedic	N OA		3					12	8		44	47			850/3541 (= 24%)
	N Spinal S										20				
	Worst case		3					12	8		64	47		134/621 (= 22%)	
	Best case		3					12	8		44	47		114/621 (= 18%)	
Neurologic	N CVA	8					6	6	3		24	38			850/3541 (= 24%)
	Worst and best case	8					6	6	3		24	38		85/705 (= 12%)	

[a]Detailed information about which diseases belong to each category of comorbidity in standard care can be found in Appendix 1. Abbreviations: CAD: coronary artery disease; CHF: congestive heart failure; High BP: high blood pressure (Hypertension); IHD: Ischemic heart disease; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitys; Dyslip: Dyslipidemia; MS: metabolic syndrome; Chol.↑: hypercholesterolemia; OA: osteoarthritis; Spinal S: Spinal stenosis; CVA: cerebrovascular disease

APPENDIX 5. JUSTIFICATION OF EXCLUSION CRITERIA.

Gardner et al. [26]:

Guidelines of the American college of Sports Medicine [42] and a study conducted by Regensteiner et al. [43] were mentioned as justification.

Hiatt et al. [29]:

Patients with diabetes mellitus were excluded because (1) the response to a conditioning program may be affected by glycemic control and (2) sever and distal distribution of arterial occlusive disease is often present in diabetic patients. As drugs may affect exercise training, patients using β-adrenergic-blocking drugs or pentoxifylline were excluded.

Hiatt et al. [30]:

Patients with diabetes mellitus were excluded because glycemic control may affect their response to exercise.

McDermott et al. [33]:

Men and women with symptoms of intermittent claudication were excluded because the aim of this study was to study the feasibility of supervised exercise therapy for symptom-free PAD patients. The following participants were considered to not likely complete a 12-week supervised exercise therapy program three times per week at the medical center and were therefore excluded: (1) individuals with above-knee and below- knee amputation; (2) individuals with a wheelchair; (3) individuals that are unable to walk without a cane or walker; (4) individuals unable to come to the medical center three times per week and (5) individuals who received cancer treatment during the preceding 6 months. As lower extremity revascularization may alter walking ability individuals scheduled for it were excluded. Individuals with angina pectoris of condition that exceeds class 2 New York Heart Association heart failure were excluded because this cardiac symptoms might limit walking ability to a greater degree than PAD. Individuals with chronic obstructive pulmonary disease (COPD) were included to enhance the generalizability of the results. For the same reason no restrictions on blood pressure or diabetes control were listed.

Mika et al. [36]:

Because there might be an effect of drugs on exercise training, patients using β-adrenergic-blocking drugs, pentoxifylline or other hemorheologically active drugs were excluded.

Mika et al. [37]:

Menopausal women and women using estrogen were excluded because both might influence high-density lipoprotein cholesterol (HDL-C) concentration

None of the other randomized controlled trials did provide justification for eligibility criteria applied.

APPENDIX 6. TREADMILL TESTING PROTOCOLS.

Gardner et al. [44]:

Subjects walk on the treadmill at an initial workload of 3.2 km/h. Subjects start with 0% incline for the first 2 minutes, which is then increased by 2% every 2 minutes without change in speed.

Hiatt et al. [45]:

Subjects walk on the treadmill at an initial workload of 2 mph (3.2km/h), 0% grade for 3 minutes. Subsequent stages increased 3.5% in grade every 3 minutes without change in speed.

Treat- Jacobson [39]:

Graded cardiopulmonary treadmill test (GXT): the GXT protocol consisted of walking on the treadmill at a speed of 2 mph (3.2km/h) at 0% grade. The treadmill grade was increased 3.5% every 3 minutes until a 10.5% grade was obtained, at which the speed was increased by 0.5 mph (0.8km/h) every 3 minutes, while maintaining the grade at 10.5%.

Chapter 6

Disease combinations associated with physical activity identified: the SMILE cohort study

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ABSTRACT

In the search for predictors of inadequate physical activity, an investigation was conducted into the association between multimorbidity and physical activity. So far the sum of diseases used as a measure of multimorbidity reveals an inverse association. How specific combinations of chronic diseases are associated with physical activity remains unclear. The objective of this study is to identify clusters of multimorbidity that are associated with physical activity. Cross-sectional data of 3,386 patients from the 2003 wave of the Dutch cohort study SMILE were used. Ward's agglomerative hierarchical clustering was executed to establish multimorbidity clusters. Chi-square statistics were used to assess the association between clusters of chronic diseases and physical activity, measured in compliance with the Dutch physical activity guideline. The highest rate of physical activity guideline compliance was found in patients the majority of whom suffer from liver disease, back problems, rheumatoid arthritis, osteoarthritis and inflammatory joint disease (62.4%). The lowest rate of physical activity guideline compliance was reported in patients with heart disease, respiratory disease and diabetes mellitus (55.8%). Within the group of people with multimorbidity, those suffering from heart disease, respiratory disease and/or diabetes mellitus may constitute a priority population as physical activity has proven to be effective in the prevention and cure of all three disorders.

INTRODUCTION

Multimorbidity, defined as the coexistence of two or more chronic diseases, is progressively more prevalent with age [1-3]. Patients with multimorbidity tend to have a poorer functional status, diminished quality of life and make more use of ambulatory and inpatient healthcare [4]. However, the growing prevalence of patients with multiple chronic diseases is not only the result of ageing and advances in medical care, but is also related to modifiable factors like unhealthy lifestyle behaviours; various studies have shown a strong association between an unfavourable lifestyle and many chronic diseases [5-7]. It is therefore important to consider lifestyle as a relevant strategy for the secondary prevention and cure of multimorbidity in patients.

Regular physical activity has proven to be effective in the prevention and cure of chronic conditions [8]. An inverse relationship has been shown between regular physical activity and cardiovascular disease, thromboembolic stroke, hypertension, osteoporosis, diabetes mellitus type II, obesity, colon cancer, breast cancer, anxiety and depression [9]. In a study of Kaplan et al. [10] the absence of thirteen chronic diseases was related to frequent physical activity. In addition to the association between physical activity and isolated chronic diseases, the association between physical activity and multimorbidity has recently been explored in older patients in a cross-sectional study by Autenrieth et al. [11]. This study showed an inverse relationship between physical activity and multimorbidity among men aged 65–94 years. We wish to stress here that the analysis of the study of Kaplan et al. [10] was based on the sum of 13 chronic diseases, while Autenrieth et al. [11] defined multimorbidity as the presence of ≥2 chronic diseases from a list of 13 diseases. Both studies used the sum of diseases as a measure for multimorbidity. Using the summation of diseases as a measure of multimorbidity has been criticised as comparing apples and oranges [12]. The resulting composite expresses multimorbidity in an additive form. A more comprehensive approach is suggested that takes into account how chronic diseases distribute and aggregate in the population, whereby any clustering of chronic diseases keeps the unique contribution of each disease salient [13]. In addition, it allows an examination of how specific combinations of chronic diseases may interact to affect physical activity behaviour. We hypothesise that certain combinations of chronic diseases may present a stronger association with physical activity as previous studies have already shown that the cumulative effect of chronic diseases is not simply additive [12]. Awareness of the association between specific combinations of chronic diseases and limited physical activity levels could facilitate the development of more targeted counselling strategies and treatment plans.

Prior work has shown an inverse relationship between the number of chronic diseases and physical activity. Yet, to our knowledge no study has assessed the association between specific disease clusters and physical activity. This study therefore goes beyond

prior work in the field of multimorbidity and investigates which clusters of multiple chronic diseases are associated with physical activity in a large representative sample of older Dutch people above 55 years of age, measured in compliance with the Dutch physical activity guideline.

METHOD

Study design and setting

This cross-sectional study is part of a dynamic prospective cohort study, the *S*tudy of *M*edical *I*nformation and *L*ifestyles in *E*indhoven (SMILE), the Netherlands. The SMILE cohort study was performed between 2002 and 2010 and was a joint project between Maastricht University and the Eindhoven Corporation of Primary Health Care Centres (SGE), including nine centres representing 32 general practitioners. Data for the SMILE cohort study was collected in two ways: (1) Information on morbidity, mortality, medication use and healthcare facility utilisation was continuously registered using electronic medical records (EMRs) in the nine primary healthcare centres; and (2) information on lifestyles and chronic diseases was collected by using annual self-administered paper questionnaires. Information on physical activity was collected annually in November. The self-reported chronic disease questionnaire was collected annually in May among all adults aged 55 years and older. The SMILE study protocol has been published [14] and approved by the medical ethics committee of the Maastricht academic hospital (MEC 07-4-030). To enhance transparency and reproducibility, this article has been written according to the STROBE checklist for cohort studies.

Participants

Registrees (12 years and older) of the participating healthcare centres were invited to participate in the overall study. All patients signed informed consent forms. Adult data (from patients aged 55 years and older) from 2003 was used in the present study since that year included the largest number of patients who completed both questionnaires (n = 3,386).

Variables

Compliance with the Dutch physical activity guideline, which states that every adult should accumulate 30 minutes or more of moderate intense physical activity (4 METs) on at least five, or preferably all, days of the week [15], was the primary outcome measurement (1 = compliance with the guideline; 0 = no compliance with the guideline). Cluster variables included the presence or absence of 15 self-reported chronic diseases. The derived clusters operated as independent variables.

Data sources/measurement

Data about the level of physical activity came from the adult questionnaire and self-reported chronic diseases data was extracted from the 55+ questionnaire.

Short QUestionnaire to ASsess Health-enhancing physical activity (SQUASH)
Physical activity was measured by the 'Short QUestionnaire to ASsess Health-enhancing physical activity (SQUASH)' [15]. Patients were asked to refer to an average week in the past few months. The SQUASH questionnaire was structured in a way that made it possible to assess compliance with the Dutch physical activity guideline. The SQUASH consists of three main queries: number of active days per week, average time per day, and intensity. All physical activities were pre-structured in (a) commuting activities, (b) leisure-time activities, (c) household activities and (d) activities at work and at school. Examples for each category of physical activity (a–d) were given as activities at work, household activities and sports. Example activities were chosen based on an intensity of 4 Metabolic Equivalents of Tasks (METs), but did not include light activities at work and light household activities. These light activities entail a considerable amount of time per day and therefore contribute to the habitual activity level. Moreover, in conformity with the SQUASH questionnaire, manual hobbies were excluded in the SQUASH due to their low MET values (~2 METs); however, hobbies that do have meaningful MET values were noted under sports.

An intensity score and a total activity score were allocated to all activities. Each activity was assigned a MET value using the Ainsworth compendium for physical activities, in which one MET is defined as the energy expenditure for sitting quietly [16]. For each intensity category, cut-off points were defined based on the Dutch physical activity guideline [15]. Activities between 1.6 and 2.9 METs were classified as light-intense, between 3 and 5.9 METs as moderate-intense, and ≥6 METs as vigorous-intense [15, 16]. The total minutes of each activity was calculated by multiplying frequency (days/week) by duration (minutes/day).

Self-reported chronic disease questionnaire
The presence or absence of 15 chronic diseases was measured using the self-reported chronic disease questionnaire. This questionnaire is based on a medical screening questionnaire of the Dutch Association of General Practitioners (LHV) [17]. Patients had to record their actual health status for the following fifteen chronic diseases: chronic bronchitis, emphysema and asthma; heart disease or myocardial infarction; severe bowel disease; liver disease or cirrhosis; severe kidney disease; diabetes mellitus; malignancy or cancer; epilepsy; migraine; stroke or stroke-related complaints; inflammatory joint disease; rheumatoid arthritis; osteoarthritis of knees, hips and hands; severe back problems, hernia, sciatica or osteoarthritis; and persistent injury from an accident

at home, in sports, school/work or traffic. Data on chronic diseases were binary (1 = a given disease is present; 0 = a given disease is absent). An open question in the questionnaire allowed patients to add other present chronic diseases that were not listed in the questionnaire. To maximise the use of available data, all chronic diseases noted in the open question (N = 1,077) were incorporated in the data gathered from the completed self-reported chronic disease questionnaires. Two researchers, assisted by a medical specialist, separately assigned the diseases noted in the open question to the existing categories in the chronic disease questionnaire (JT).

Bias

Cluster analysis algorithms assume that there are no missing values. Solutions are developed if values are missing; however, these are only technically valid if the values are missing completely at random (MCAR). In the self-reported chronic disease questionnaires, missing values are observed ranging from 592 (17.5%) for epilepsy to 818 (24.2%) for inflammatory joint disease. We assume that these missing values are not completely random (MNAR) [18], but are the result of inadequate instructions being provided with the chronic disease questionnaire. Patients were asked to indicate in a dichotomous pre-structured form (yes/no) which of the 15 chronic diseases they suffer from. The hypothesis is that a proportion of patients followed this instruction by only indicating the presence of a certain disorder without explicitly registering the absence (by ticking 'no') of all other diseases listed. Following this hypothesis, all missing values for the 15 chronic diseases were interpreted and recoded as 'disease being absent'.

Statistical analysis

The aim of the analysis was to identify clusters of chronic diseases based on their relative similarity or dissimilarity (distance). Cluster analysis is used because it best fits the aim of our study, namely to identify meaningful groups of patients with chronic diseases. Because there is not a one-and-only valid approach to establish groups of patients in relation to chronic diseases, the two most frequently applied forms of clustering, namely Ward's agglomerative hierarchical clustering and K-means clustering were used.

First, the most widely used form of clustering [18-20], Ward's agglomerative hierarchical clustering, applying squared Euclidean distance as a similarity measure, was performed. Each individual disease starts as an individual cluster which is then gradually agglomerated with the next most similar cluster on the basis of a proximity measurement using a predefined fusion algorithm [19]. Distances are recalculated and diseases reassigned until all are in a single cluster. Robust groups of chronic diseases are obtained at the point where the individual clusters are as homogeneous as possible within clusters and as heterogeneous as possible in relation to the other clusters [20]. As the number of clusters was not known a priori, a series of cluster analyses with predefined

cluster numbers ranging from 2 to 5 was performed. The agglomerative coefficient, the dendogram and the pseudo-F statistic were used to determine the appropriate number of clusters. The pseudo-F statistic (ratio of the mean sum of squares between groups to the mean sum of squares within groups [20]) was calculated to capture the 'tightness' of clusters. The following formula was used to calculate the pseudo-F statistic:

$$\text{Pseudo-F} = \frac{(SS(T) - SS(W))/ (N-1)}{SS(W)/ (n- N)}$$

In the above formula, SS(T) is the total sum of squares, SS(W) is the within-group sum of squares and N is the number of clusters. A larger pseudo-F statistic indicates a better cluster solution. Second, based on the findings obtained from using Ward's agglomerative hierarchical clustering, a K-means cluster analysis was executed to check our findings. Unlike the hierarchical clustering method, K-means starts by assigning patients randomly to one cluster and proceeds with iteration. Patients were gradually reassigned to minimise the within-cluster variation. This iteration was continued until the smallest within-cluster variation was reached. One thousand combinations of random starts were investigated. Cross-tabulation using Chi-square statistics was performed to assess the association between established clusters of chronic diseases and compliance with the Dutch physical activity guideline. To get full insight into the association between multimorbidity and physical activity and to study the consequences of branching of clusters Ward's two- to five cluster solution will be studied. Disease frequency distributions within each cluster were evaluated using crosstabs. The sociodemographic characteristics of all patients belonging to each cluster in each cluster solution were determined using descriptive and frequency statistics.

RESULTS

Participants

Both the general adult questionnaire and the additional 55+ questionnaire were returned by 3,386 patients.

Table 1. Characteristics of the study population

Characteristics[a]	Total population *N* = 3,386	Males (47.1%) *n* = 1,595	Females (52.9%) *n* = 1,791
Age (years)	67.5 ± 8.3	67.5 ± 8.2	67.5 ± 8.4
Length (cm)	170.0 ± 8.8	176.2 ± 6.6	164.3 ± 6.5
Body weight (kg)	75.1 ± 13.8	80.4 ± 13.3	70.3 ± 12.3
Chronic bronchitis, emphysema and asthma	321 (9.5)	148 (9.3)	173 (9.2)
Heart disease or myocardial infarction	299 (8.8)	180 (11.3)	119 (6.6)
Severe bowel disease	112 (3.3)	51 (3.2)	61 (3.4)
Liver disease or cirrhosis	16 (0.5)	9 (0.6)	7 (0.4)
Severe kidney disease	48 (1.4)	25 (1.6)	23 (1.3)
Diabetes mellitus	230 (6.8)	122 (7.6)	108 (6.0)
Malignancy	77 (2.3)	44 (2.8)	33 (1.8)
Epilepsy	20 (0.6)	7 (0.4)	13 (0.7)
Migraine	158 (4.7)	52 (3.3)	106 (5.9)
Stroke or stroke-related complaints	70 (2.1)	35 (2.2)	35 (2.0)
Inflammatory joint disease	302 (8.9)	115 (7.2)	187 (10.4)
Rheumatoid arthritis	150 (4.4)	43 (2.7)	107 (6.0)
Osteoarthritis of knees, hips or hands	780 (23.0)	290 (18.2)	490 (27.4)
Severe back problems, hernia, sciatica or osteoarthritis	517 (15.3)	239 (15.0)	278 (15.5)
Persistent injury from an accident at home, in sports, school/work	132 (3.9)	61 (3.8)	71 (4.0)

[a] Dichotomous variables are presented as N (%) and continuous variables as the mean ± standard deviation.

Fifty-three per cent were female and the average age of patients was 68 years (range: 55–95 years). The average length and bodyweight of patients was 1.70m (range: 1.41–1.99m) and 75kg (range: 40kg–185kg), respectively. Osteoarthritis of knees, hips and hands was the most prevalent disease (23%). The prevalence of heart disease or myocardial infarction was approximately twice as high in males as in females (11.3% versus 6.6%, respectively). In comparison, musculoskeletal disorders like inflammatory joint disease (7.2% versus 10.4%), rheumatoid arthritis (2.7% versus 6.0%) and osteoarthritis of knees, hips and hands (18.2% versus 27.4%) were less prevalent among females

compared with males. Prevalence rates of all fifteen chronic diseases from the SMILE cohort (measured in the Eindhoven region) were comparable with national prevalence rates in Dutch older adults [21, 22].

Multimorbidity clusters

Two-cluster solution

For Ward's agglomerative hierarchical clustering, the stepwise agglomerative coefficients and the pseudo-F statistic suggested a two-cluster solution being most feasible (Table 2). K-means clustering displayed consistent results, with the Sum of Squares (SS) being 2177.8 and pseudo-F being 1318.4.

Table 2. Agglomerative coefficient and pseudo-F statistic for hierarchical clustering

No. of clusters	Agglomeration last step	Coefficient current step	Score change	Pseudo-F	p-value
2	2847.045	2516.781	330.264	1533.167[b]	0.000
3	2516.781	2307.600	209.181[a]	767.332	0.000

[a] Demarcation point -> 2 clusters

[b] Ratio of between-cluster variance to within-cluster variance largest -> 2 clusters

Figure 1 shows for each disease how the patients (i.e., the patients that have the disease in question) are distributed across the two clusters. For instance, the first bar in the figure shows that of the patients who have chronic bronchitis, emphysema and asthma, 10% are assigned to cluster one and 90% are part of cluster two. Detailed information about the importance and distribution of each chronic disease in the clustering can be found in Appendix 1.

Of the patients who have severe bowel disease 96.4% is included in cluster one. Of the patients with severe kidney disease or cancer also the majority is involved in cluster one (85.4% and 81.1%, respectively). Similarly of the patients with epilepsy (65.0%), migraine (71.5%), stroke or stroke-related complaints (87.1%), and persistent injury from an accident at home, in sports, school/work or traffic (80.3%) the majority is a member of the first cluster. In other words, cluster one is the dominant cluster for severe bowel disease, severe kidney disease, cancer, epilepsy, migraine, stroke and persistent injury from an accident.

Cluster two is dominated by respiratory disease, heart disease, liver diseases, diabetes mellitus, inflammatory joint disease, rheumatoid arthritis, osteoarthritis and severe back problems. Of the patients with chronic bronchitis, emphysema and asthma 90.0% are in cluster two. Of the patients with myocardial infarction 89.0% are in cluster two and 81.3% of the patients suffering from liver disease or cirrhosis are included in the

second cluster. The majority of the patients with diabetes mellitus (87.4%), inflammatory joint disease (92.1%), rheumatoid arthritis (92.0%), osteoarthritis of knees, hips, hands (84.7%) and severe back problems, hernia, sciatica or osteoarthritis (82.3%) are also member of cluster two.

A resumed description of the two clusters is also presented in Figure 2.

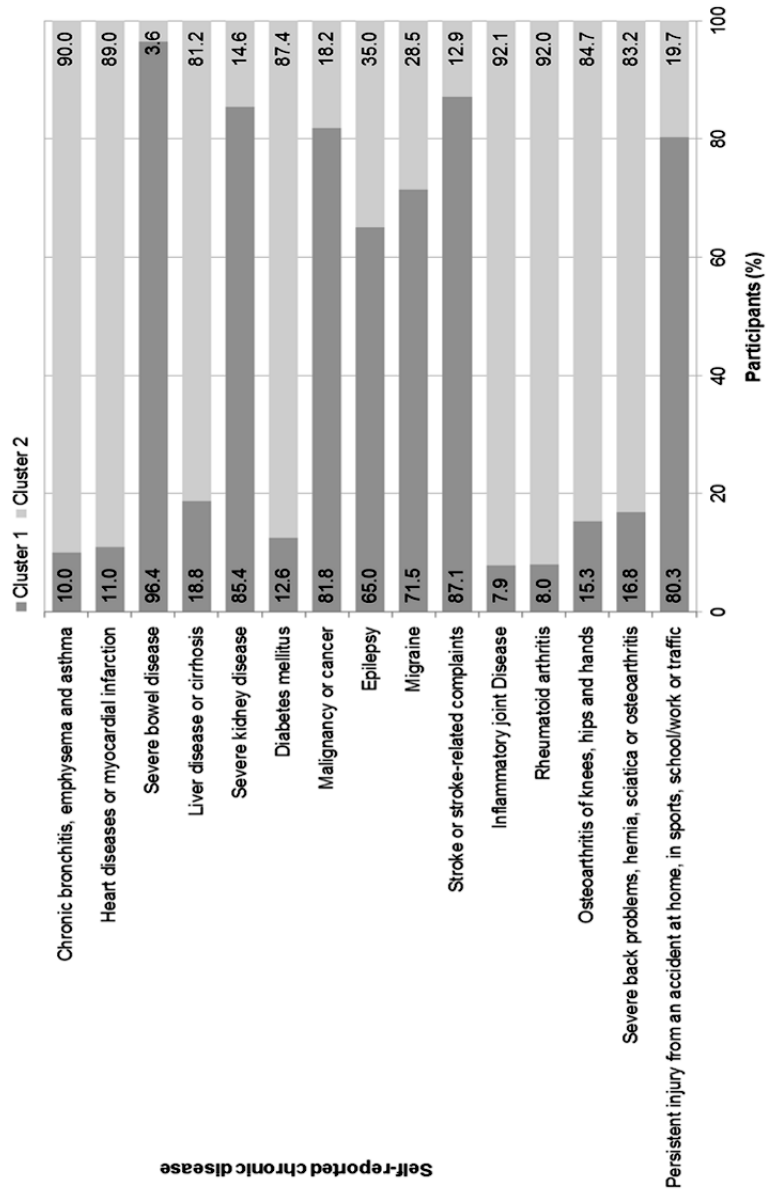

Figure 1. The distribution of patients that suffer from one of the 15 chronic diseases across the two clusters

Association between clusters and physical activity

Two-cluster solution

Of the total of 3,386 patients, 60.8% (*N* = 2,060) complied with the Dutch physical activity guideline. Of the people belonging to cluster one, 61.8% complied with the Dutch physical activity guideline, and of the people belonging to cluster two, 59.4% complied with this guideline. The proportion of respondents that complied with the Dutch physical activity guideline was not significantly different between the two clusters (Chi-square: 1.847; p = 0.174).

Although statistically a two-cluster solution was identified as being most optimal, the aim of this study was to discover the combination of diseases that not only cluster but also interact with physical activity. To explore whether further branching of clusters might provide information regarding the relationship between clusters and physical activity, analysis proceeded with a Ward's three-cluster solution.

Multimorbidity clusters

Three-cluster solution

The results of the Ward's three-cluster solution are presented in Figure 2, with Ward's two and three-cluster solutions shown on the horizontal axis. The boxes below each cluster solution represent the clusters and contain the diseases in each cluster. Ward's three-cluster solution showed that the first cluster remained the same while cluster two separated further (Figure 2). The third cluster contained patients the majority of whom had heart disease or myocardial infarction (77.6%), diabetes mellitus (83.9%) and/or chronic bronchitis, emphysema and asthma (82.9%).

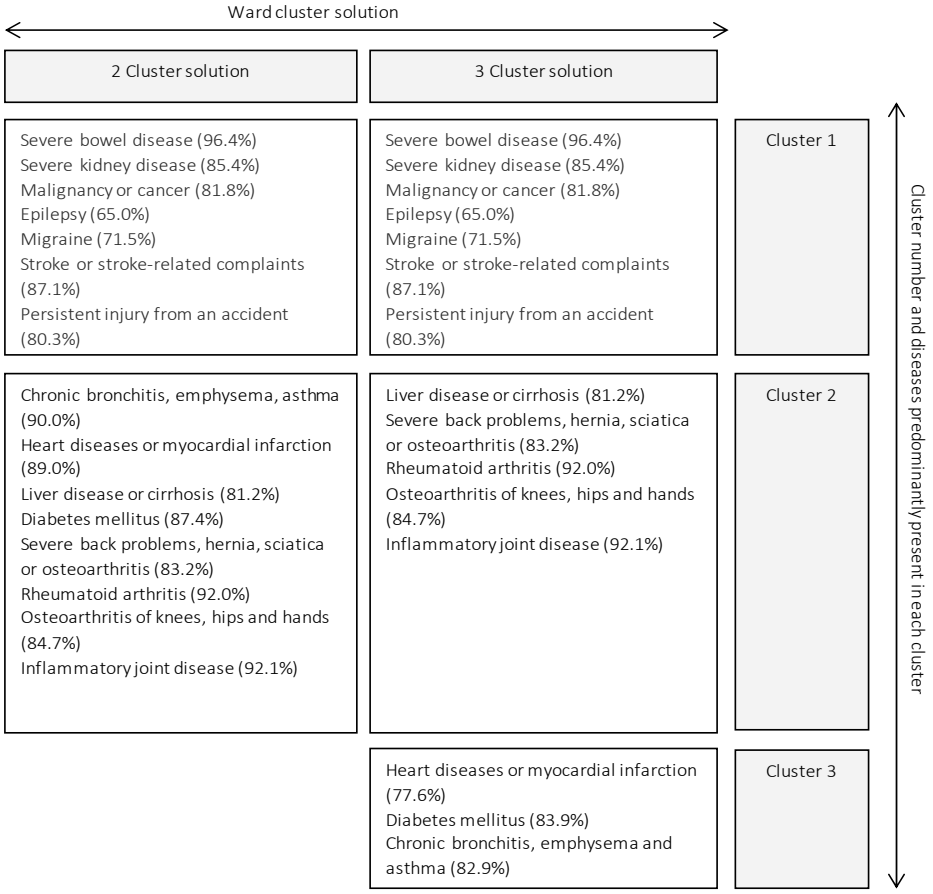

Figure 2. Description of identified clusters according to Ward's agglomerative hierarchical two and three-cluster solution

Association between clusters and physical activity

Three-cluster solution

The proportion of adults that comply with the Dutch physical activity guideline is highest in cluster two (62.4%), followed by cluster one (61.8%) and finally cluster three (55.8%). The relationship between the three-disease clusters and physical activity guideline compliance was statistically significant (Chi-square: 7.968; p = 0.019; Figure 3).

Ward's four-cluster solution led to a cluster containing a single disease (heart disease). First, because a single disease does not represent a multimorbidity cluster and hence does not fit the aim of the present study, clustering was stopped after Ward's three-cluster solution. Second, all other clusters presented in the four cluster solution were comparable which supports our decision to stick to the three-cluster solution (Appendix 2).

DISCUSSION

The aim of the present study was to assess the relationship between multimorbidity clusters and compliance with the Dutch physical activity guideline. The two-cluster solution showed no significant association with physical activity guideline compliance. Further exploration revealed a significant relationship between three multimorbidity clusters and physical activity. The highest rate of physical activity guideline compliance (62.4%) was found in cluster two, of which the majority of patients had liver disease, back problems, rheumatoid arthritis, osteoarthritis and inflammatory joint disease. The lowest rate of physical activity guideline compliance (55.8%) was reported in patients with heart disease, respiratory disease and diabetes mellitus. Compared with the average Dutch proportion of older adults (e.g. 68.6% [21, 22]), fewer people adhered to the Dutch physical activity guideline in all three clusters.

The main limitation of the present study is its cross-sectional design, which prevents the establishment of any causal inference. The quantity of missing values ranging from 17.5% (epilepsy) to 24.2% (inflammatory joint disease) in the self-reported chronic disease questionnaire formed a limitation. To obtain as much information as possible, we interpreted missing values as absence of the disease, and this may have caused the disease burden in this population to have been underestimated. As a control, patient characteristics were checked, revealing comparable results for patients with and without missing data on chronic diseases. Furthermore, the presence of chronic diseases was measured via a self-reported questionnaire, and one may well wonder whether a patient is able to report this information adequately. Informed consent issues prevented us from being able to check the self-reported data against data registered in electronic medical records (EMRs). Nevertheless, previous research on the SMILE cohort identified a high level of agreement between self-reports of chronic diseases and information from electronic medical records [23]. The high level of agreement between medical records and patients' reports in this large community-based cohort supports the accuracy of self-reported data used in answering the research question. The self-reported chronic disease questionnaire could be considered limited and without any assessment of disease severity, and this may have led to an under or overestimation of the true burden of chronic diseases. Moreover, people tend to overestimate their physical activity level [24], which might have introduced another systematic bias. Also not considered were seasonal influences that could influence the amount of physical activity performed. Yet, the SQUASH questionnaire represents a reliable and valid measurement instrument for population samples [15]. Finally, while a measure of social desirability may also have influenced the patients' answers, the respondents remained anonymous to researchers and were assured that their information would not be reported to their general practitioner. Despite these limitations, this study is the first to examine the relationship between clusters of chronic diseases and physical activity.

The first analysis revealed two clusters for which no association with physical activity was detected. The clusters found were broad (representing at least seven diseases) and diverse in terms of types of the diseases embodied in each cluster. As previous research had shown an inverse relationship between multimorbidity and physical activity, the question which specific disease combinations are associated with physical activity remained unanswered. Therefore, the exploration was continued with the three-cluster solution and we found that only the initial second cluster had branched out into two new ones. The results of the three-cluster solution showed that cluster one remained unchanged and that heart disease, respiratory disease and diabetes had separated from the original cluster two to form a third cluster. The relationship between the three-cluster solution and physical activity was significant. The third cluster had the lowest proportion of people who were compliant with the Dutch physical activity guideline. The highest proportion of people who were compliant was found in cluster two, which had a compliance proportion similar to cluster one.

As people in cluster three showed lower activity levels on average, it might be worthwhile to examine the diseases found in this cluster, namely heart disease, respiratory disease and diabetes mellitus. It may not be surprising that this combination of diseases formed a separate cluster given that they are highly prevalent diseases that have been shown to be interrelated. For example, Howard et al. [25] estimated that the relative risk of developing cardiovascular disease is two-to-eight times higher in people with diabetes mellitus compared with non-diabetics. The relationship between respiratory disease and cardiovascular disease seems to be related to systemic inflammation and chronic infections [26]. Systemic inflammation also seems to contribute to the triangle association as there seems to be increased inflammatory markers in diabetes mellitus and respiratory disorders. Reactive Oxygen Species (ROS) injure the airways and promote inflammation, and are considered an underlying cause of insulin resistance. Moreover, all three diseases may be intimately intertwined because they share the same risk factors (e.g. smoking, obesity, hyperlipidaemia and hypertension) [27].

The fact that the diseases in cluster three showed the lowest proportion of physical activity guideline compliance could be expected. The inverse relationship between cardiovascular disease, respiratory disease and diabetes mellitus, as individual disorders, and physical activity has been studied extensively [25-27].

To our knowledge, only four studies have until now investigated the relationship between multimorbidity and physical activity [10, 11, 28, 29]. Three of these four studies found an inverse relationship between multimorbidity and physical activity levels [10, 11, 29]. The results of these studies concur with those presented by Hudon et al. [28] who reported that multimorbidity was not associated with physical activity levels. Measurement differences in the assessment of multimorbidity and physical activity challenge the comparability of results. First, regarding the estimation of chronic diseas-

es, correspondence existed as all four studies used self-reported data and counted the number of chronic diseases. Nevertheless, the chronic diseases listed in the survey or questionnaire and the cut-off point of the disease count defining multimorbidity were dissimilar. Second, differences in physical activity measurement might have contributed to the variation observed in the results as physical activity is a complex and multidimensional dependent variable which makes population-based measurement difficult. Kaplan et al. [10] asked patients to report the number of times in the past month that they had taken part in recreational physical activity lasting ≥ 15 minutes. Similarly, Hudon et al. [28] measured physical activity by the number of recreational physical activity sessions of 20–30 minutes during the preceding three months. The PASE, an instrument that measures the level of physical activity for individuals aged 65 years and older, was used in the study of Autenriet et al. [11]. The PASE is comprised of self-reported occupational, household and leisure items over a one-week period. However, to reach sufficient content validity Poppel et al. [30] recommended in 2010 (after the study of Kaplan et al. [10] and Hudon et al. [28] had been published, but before Autenrieth and colleagues started their investigation) that each questionnaire assessing total physical activity should at least measure duration and frequency in all settings (household, work, transport, recreation and sport). Both the International Physical Activity Questionnaire (IPAQ) used by Cimarras-Otal et al. [29] and the Short Questionnaire to Assess Health-enhancing physical activity (SQUASH), which was used in this study, follow this recommendation. The IPAQ and the SQUASH questionnaires allow for a more detailed assessment as they include questions on activity frequency, duration and intensity and make it possible to determine if a person meets the current recommendation for physical activity. It is important to emphasise that multimorbidity was classified into categories (0, 1, 2, and ≥ 3 diseases) in all four previously conducted studies. This study is the first which explores the relationship with physical activity using chronic disease clusters. Investigating the relationship between the number of chronic diseases and compliance with the Dutch physical activity guideline in the present SMILE cohort study revealed a statistically significant inverse relationship ($p = 0.004$). Although, we specifically chose for cluster analysis because content-wise it fitted our primary aim best, other data reduction methods and procedures are expected to reveal comparable groups of patients [31, 32].

In conclusion, this study adds to our knowledge of the relationship between multimorbidity and physical activity. In addition to the inverse relationship of the number of chronic diseases and physical activity, the present study showed that the cluster of patients with cardiovascular disease, respiratory disease and/or diabetes type II reported the lowest physical activity levels. Belonging to a specific cluster of diseases does make a difference and it is important for general practitioners and physiotherapists to help especially patients with cardiovascular disease, respiratory disease and/or diabetes to initiate and maintain appropriate physical activity levels. It seems worthwhile to fur-

ther explore the relationship between multimorbidity clusters and outcomes like physical activity, because it helps to deliver more targeted and effective care for patients.

Acknowledgements

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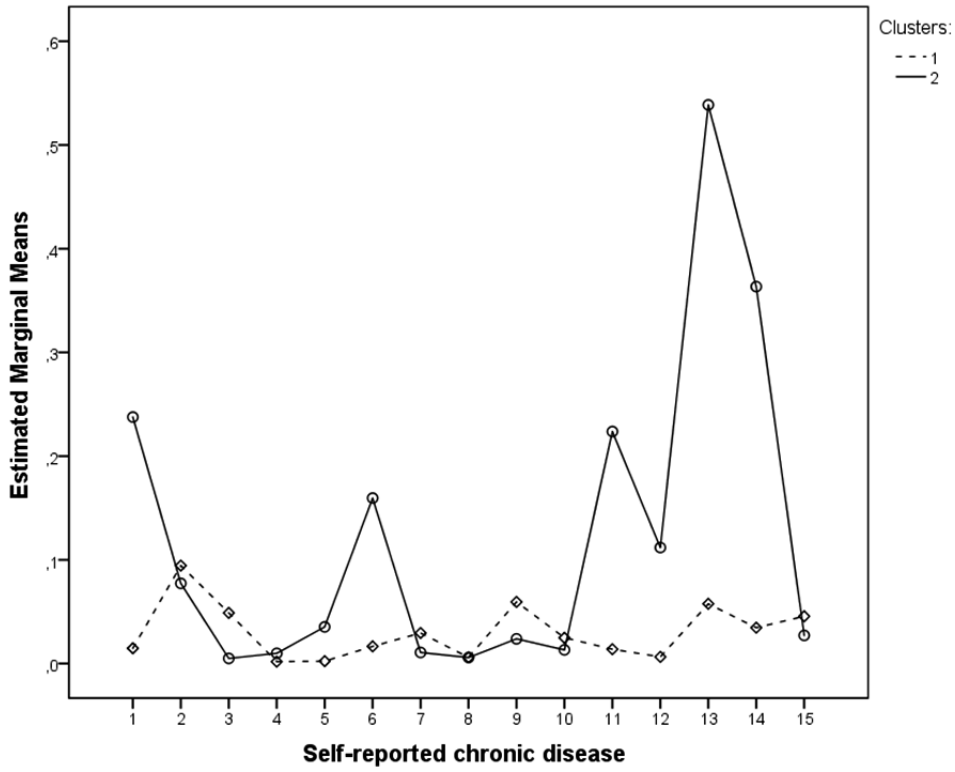
APPENDIX

APPENDIX 1. IMPORTANCE AND DISTRIBUTION OF EACH CHRONIC DISEASE IN THE CLUSTERING



Self-reported chronic disease[a]

1	Chronic bronchitis, emphysema and asthma	9	Migraine
2	Heart disease or myocardial infarction	10	Stroke or stroke-related complaints
3	Severe bowel disease	11	Inflammatory joint disease
4	Liver disease or cirrhosis	12	Rheumatoid arthritis
5	Severe kidney disease	13	Osteoarthritis of knees, hips and hands
6	Diabetes mellitus	14	Severe back problems, hernia, sciatica or osteoarthritis
7	Malignancy or cancer	15	Persistent injury from an accident at home, in sports, school/work
8	Epilepsy		

[a] For the ease of presentation self-reported chronic diseases were listed as number 1 to 15 in the graph.

Figure 1. The proportion of patients as a function of chronic disease and cluster division

Figure 1 shows a plot of the cluster centroids with each disease being a cluster variable. These cluster centroids show for each chronic disease (1-15) and for each cluster (dot-

ted and straight line) the proportion of patients (i.e., subjects who have the disease in question). To illustrate, the proportion of subjects with chronic bronchitis, emphysema and asthma is higher in cluster two compared to cluster one. Moreover, based on these proportions one may identify which chronic diseases are most important in distinguishing between the two clusters of subjects. Cluster one and two differ predominantly with regard to the proportion of occurrence of chronic bronchitis, emphysema and asthma (21.5% versus 1.6%, respectively); heart diseases or myocardial infarction (1.6% versus 19.8%, respectively); diabetes mellitus (1.4% versus 14.9%, respectively); inflammatory joint disease (1.2% versus 20.7%, respectively); osteoarthritis of knees, hips, hands (5.8% versus 49.1%, respectively) and severe back problems, hernia, sciatica or osteoarthritis (4.3% versus 31.9%, respectively).

APPENDIX 2. IDENTIFIED CLUSTERS ACCORDING TO THE TWO-TO FIVE CLUSTER SOLUTION

Ward cluster solution

2 Cluster solution	3 Cluster solution	4 Cluster solution	5 Cluster solution	Cluster number and diseases predominantly present in each cluster
Severe bowel disease (96.4%) Severe kidney disease (85.4%) Malignancy or cancer (81.8%) Epilepsy (65.0%) Migraine (71.5%) Stroke or stroke-related complaints (87.1%) Persistent injury from an accident (80.3%)	Severe bowel disease (96.4%) Severe kidney disease (85.4%) Malignancy or cancer (81.8%) Epilepsy (65.0%) Migraine (71.5%) Stroke or stroke-related complaints (87.1%) Persistent injury from an accident (80.3%)	Severe bowel disease (96.4%) Severe kidney disease (85.4%) Malignancy or cancer (81.8%) Epilepsy (65.0%) Migraine (71.5%) Stroke or stroke-related complaints (87.1%) Persistent injury from an accident (80.3%)	Severe bowel disease (96.4%) Severe kidney disease (85.4%) Malignancy or cancer (81.8%) Epilepsy (65.0%) Migraine (71.5%) Stroke or stroke-related complaints (87.1%) Persistent injury from an accident (80.3%)	Cluster 1
Chronic bronchitis, emphysema, asthma (90.0%) Heart diseases or myocardial infarction (89.0%) Liver disease or cirrhosis (81.2%) Diabetes mellitus (87.4%) Severe back problems, hernia, sciatica or osteoarthritis (83.2%) Rheumatoid arthritis (92.0%) Osteoarthritis of knees, hips and hands (84.7%) Inflammatory joint disease (92.1%)	Liver disease or cirrhosis (81.2%) Severe back problems, hernia, sciatica or osteoarthritis (83.2%) Rheumatoid arthritis (92.0%) Osteoarthritis of knees, hips and hands (84.7%) Inflammatory joint disease (92.1%)	Liver disease or cirrhosis (81.2%) Severe back problems, hernia, sciatica or osteoarthritis (83.2%) Rheumatoid arthritis (92.0%) Osteoarthritis of knees, hips and hands (84.7%) Inflammatory joint disease (92.1%)	Rheumatoid arthritis (92.0%) Osteoarthritis of knees, hips and hands (84.7%) Inflammatory joint disease (92.1%)	Cluster 2
	Heart diseases or myocardial infarction (77.6%) Diabetes mellitus (83.9%) Chronic bronchitis, emphysema and asthma (82.9%)	Heart diseases or myocardial infarction (69.6%)	Heart diseases or myocardial infarction (69.6%)	Cluster 3
		Chronic bronchitis, emphysema and asthma (74.5%) Diabetes mellitus (81.7%)	Chronic bronchitis, emphysema and asthma (74.5%) Diabetes mellitus (81.7%)	Cluster 4
			Liver disease or cirrhosis (62.5%) Severe back problems, hernia, sciatica or osteoarthritis (51.8%)	Cluster 5

Figure 2. Description of identified clusters according to Ward's agglomerative hierarchical two- to five cluster solutions.

Chapter 7

Synergistic effects of Six Chronic Disease Pairs on Decreased Physical Activity: the SMILE cohort study

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ABSTRACT

Physical inactivity is a global public health problem. One aim of the World Health Organization's (WHO) strategy to increase physical activity (PA) in the European Region from 2016 to 2025 is to promote PA behaviour in order to drastically reduce the number of people suffering from non-communicable diseases. Although, most chronic diseases are associated with physical inactivity, little is known about whether two chronic diseases might interact with each other in modifying the risk of physical inactivity. Our main research interest was to investigate whether certain disease pairs/combinations indicate an 'extra' additional effect, on top of the effects of the diseases separately/individually. The first aim of the present study is to identify chronic disease pairs that are associated with compliance or non-compliance with the Dutch PA guideline recommendation. The second aim is to study whether specific chronic disease pairs indicate an additional/extra (interaction) effect on top of the effects of the diseases separately/individually. Cross-sectional data from 3,386 participants of the prospective Dutch cohort study SMILE were used. Chi-Square statistics were used to test whether there was an inverse association between 105 chronic disease pairs and compliance with the Dutch PA guideline. Logistic regression analysis was performed to study the joint effect of the two diseases of each chronic disease pair for compliance with the Dutch PA guideline. The results showed that the interaction term of six chronic disease pairs was statistically significant, which means that the effect of the two diseases combined is not additive. Furthermore, in all six cases the odds ratio of the interaction term is larger than one, which means that patients suffering from both diseases of the pair in question have an increased risk for non-compliance with the Dutch PA guideline recommendation compared to what one would expect based on the effects of each of the two diseases alone. The disease pairs in question were chronic respiratory disease and severe back problems; migraine and inflammatory joint disease; chronic respiratory disease and severe kidney disease; chronic respiratory disease and inflammatory joint disease; inflammatory joint disease and rheumatoid arthritis; and rheumatoid arthritis and osteoarthritis of the knees, hips and hands. The results of the present study may alert health care professionals of extra low physical activity levels in patients with one of these six chronic disease pairs.

KEYWORDS

Public health, physical inactivity, ageing, multimorbidity, chronic disease, prevention, treatment

INTRODUCTION

Inspired by Health 2020 [1], the first World Health Organization (WHO) strategy to tackle physical inactivity in the European Region from 2016 to 2025 was released last September. The aim of this strategy is to inspire governments and stakeholders to promote physical activity levels among all citizens in the European Region. The rationale for this effort was that health care systems are at risk of being inundated by large numbers of people suffering the effects insufficient physical activity, such as coronary heart disease, hypertension, colon cancer and diabetes mellitus [2]. Suffering from a disease is a risk factor in the downward spiral of PA, especially among those suffering from more than one chronic disease [3, 4].

To date, most studies that investigated the association between chronic disease and PA are limited to one chronic disease in particular, thus avoiding the actual complexity [5-8]. From previous literature we know that patients with chronic diseases and/or multimorbidity are at risk for physical inactivity [1-4]. For clinicians and physical therapists it is particularly important to identify patients with specific combinations of chronic diseases that are at risk for extra physical inactivity, so that more conscious approaches to initiate or increase physical activity in these patients can be applied. Although, most chronic diseases are associated with physical inactivity, little is known about whether two chronic diseases might interact with each other in modifying the risk of physical inactivity. Since the effect of two chronic diseases on physical inactivity might not always be simply additive it is important to highlight those chronic disease pairs for whom the effect of both diseases on physical inactivity is greater than the sum of the individual effects alone. Our main research interest was to investigate whether certain disease pairs/combinations indicate an 'extra' additional effect, on top of the effects of the diseases separately/individually. We hypothesized that exposure to a specific combination of chronic diseases had additional/extra (interaction) effects on the risk of inadequate physical activity levels above what would be expected from either exposure alone.

The present study has two aims, based on the observation that chronic disease pairs provide information about how combinations of diseases behave and how they may be associated with PA. The first aim is to identify chronic disease pairs that are associated with compliance or non-compliance with the Dutch PA guideline recommendation and the second, to investigate whether specific chronic disease pairs indicate an additional/extra (interaction) effect on top of the diseases separately/individually. A portion of the data from the large prospective cohort Study of Medical Information and Lifestyles in Eindhoven (SMILE), the Netherlands was used for the present study [11].

METHOD

Study design and setting

The present study used a portion of the data from the prospective dynamic cohort SMILE, the Netherlands [11]. The SMILE study focuses on different aspects of disease, health and lifestyle and is a joint project between Maastricht University and 23 General Practitioners from nine Primary Healthcare Centres of the Eindhoven Corporation of Primary Health Care Centers (Stichting Gezondheidscentra Eindhoven (SGE)) in Eindhoven. The SMILE cohort study was conducted between 2002 and 2010. One goal of SMILE is to study diseases and their consequences. In the SMILE cohort study two data collection strategies were combined. With the help of electronic medical records (EMRs), data on morbidity, mortality, medication and care facility utilisation were registered. Information on lifestyle and chronic diseases was gathered on the basis of patient questionnaires which were self-administered and completed on paper. Detailed information on the study protocol can be found in a publication by van den Akker et al. [11]. The SMILE protocol was approved by the medical ethics committee of the Academic Hospital Maastricht (MEC 07-04-030) and all participants signed written informed consent forms [11]. This article was written according to the *ST*rengthening the *R*eporting of *OB*servational studies in *E*pidemiology (STROBE) checklist for cohort studies in order to enhance transparency and reproducibility.

Participants

Data of adult patients aged 55 from 2003 were used, as the numbers of patients who returned their information on chronic diseases and PA behaviour (n = 3,386) was largest for that cohort year.

Data sources/measurement

All participants completed two questionnaires. Information on chronic diseases was measured using a self-reported chronic disease questionnaire [13] which was distributed and returned in May 2003. Physical activity behaviour was measured using the *S*hort *Que*stionnaire to *As*sess *H*ealth-enhancing physical activity (SQUASH) [12]. Data from the SQUASH questionnaire was gathered in November 2003.

Self-reported chronic disease questionnaire

Information about the presence/absence of chronic disease was obtained from the self-reported chronic disease questionnaire, for which the medical screening questionnaire of the Dutch Association of General Practitioners (Landelijke Huisartsen Vereniging (LHV)) served as a template [8]. Participants were asked to report whether they had any of the

following fifteen chronic diseases at that time: (1) chronic respiratory disease; (2) cardiovascular disease; (3) severe bowel disease; (4) liver disease; (5) severe kidney disease; (6) diabetes mellitus; (7) cancer; (8) epilepsy; (9) migraine; (10) neurological disorders and stroke; (11) inflammatory joint disease; (12) rheumatoid arthritis; (13) osteoarthritis of the knees, hips and hands; (14) severe back problems; and (15) persistent injuries due to accidents. Furthermore, in response to an open question, patients could report other diseases they had which were not listed in the questionnaire. The chronic diseases mentioned in response to this open question (N= 1,077) were integrated into the questionnaire data. Two researchers (SD and IM) and one medical specialist (JT) independently assigned each disease to the existing categories of the chronic disease questionnaire.

Short Questionnaire to Assess Health-enhancing physical activity (SQUASH)
The SQUASH questionnaire was used to measure PA [12]. This questionnaire asked three main questions: 1) how many days per week one was active, 2) average time of activity per day and 3) PA intensity. Therefore it was possible to assess compliance with the Dutch PA guideline with this questionnaire. Participants were asked to report their level of PA during an average week over the past few months. To simplify reporting, the questionnaire was subdivided into (a) commuting activities, (b) leisure time activities, (c) household activities and (d) activities at work and at school. Using the Ainsworth compendium for physical activities, a MET value was assigned to each activity [14, 15]. Activities between 1.6- 2.9 METs were classified as light-intense, activities between 3.0- 5.9 METs as moderate-intense and activities ≥ 6 METs as vigorous-intense [15]. To determine compliance with the Dutch PA guideline, the frequency, duration and intensity of each activity were multiplied by each other.

Variables

Chronic disease pairs were used as an independent variable. Disease pairs were constructed based on the fifteen chronic diseases listed in the self-reported chronic disease questionnaire. All possible combinations of two chronic diseases were established. The primary outcome was compliance with the Dutch PA guideline (0= compliance with the guideline, 1= lack of compliance with the guideline). This guideline states that all adults should participate in a total of at least 30 minutes of moderate intense PA at least five days a week, but preferably daily [16].

Bias

Of the 15 chronic diseases listed in the self-reported chronic diseases questionnaire, missing values amounting to some 17.5% to 24.2% were detected. The format of the questionnaire was dichotomous and pre-structured (yes/no). The hypothesis is that a proportion of respondents followed these instructions to the letter and only indicated the dis-

eases they had without explicitly indicating which ones they did not suffer from (i.e. by ticking 'no'). Therefore, all missing values were recorded as 'disease being absent'.

Statistical analysis

First, from the fifteen chronic diseases listed in the self-reported chronic disease questionnaire, a number of 105 (N*[(N-1)/2]) disease pairs (disease A + disease B) was calculated (Appendix 1). The occurrence of diseases pairs was calculated and pairs that affected fewer than 10 participants were excluded from the analysis in order to maximise the chance of showing an association with compliance with the Dutch PA guideline. Pearson's Chi-square test was used to test whether patients having the combination of two diseases show higher probabilities of non-compliance compared to the other patients. The alpha was set at <0.10 to give room for the detection of all chronic disease pairs associated with PA that might be relevant for clinical practice. For all cross tables with a value $N \leq 5$ in at least one of the cells, Fisher's Exact was used as alternative for the Chi-square [17]. Significant chronic disease pairs were listed and were the subject of further analysis (N=14; Figure 1).

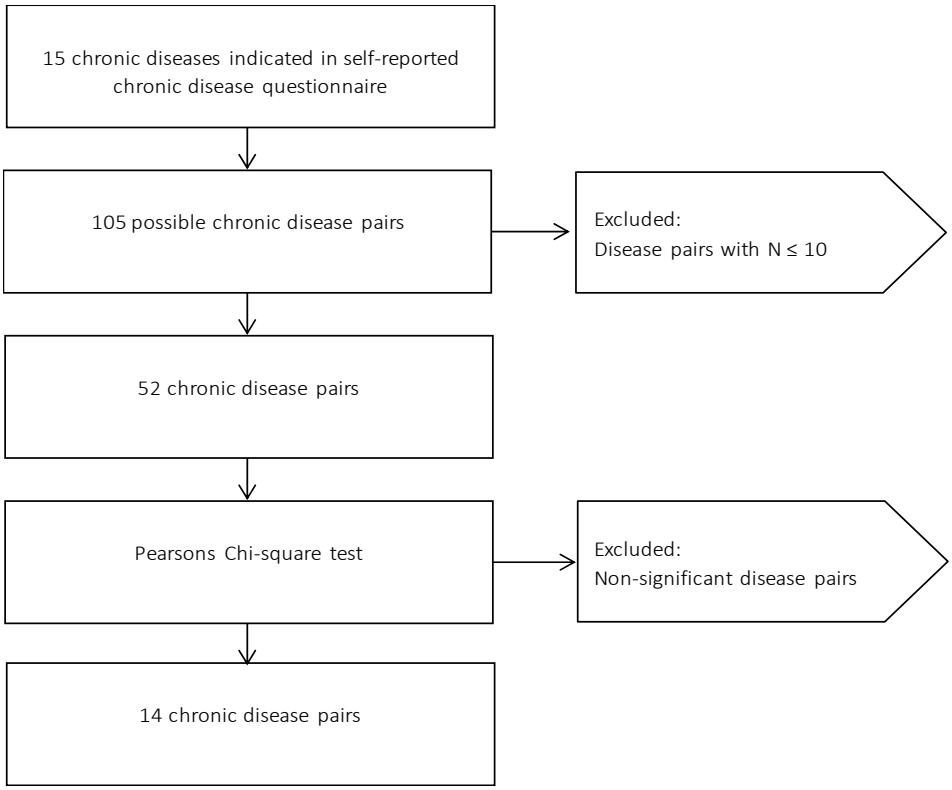


Figure 1. Flowchart of the selection of chronic disease pairs

The second aim of the present study was to study whether the association between chronic disease pairs and PA guideline compliance surpasses the expected result of the combined effects of both diseases individually. Logistic regression analyses were performed to study the joint effect of the two diseases of each chronic disease pair for compliance with the Dutch PA guideline. Compliance with the Dutch PA guideline (1= lack of compliance with the guideline; 0= compliance with the guideline) was used as a dependent variable. Independent variables included the two indicator variables that represent occurrence of the two diseases of the pair as well as the product of these two indicator variables in order to capture a potential interaction effect. Main effects of each disease separately/individually are not presented, but can be read from the model: the simple main effect of A (in terms of an odds ratio) for B = 1 is equal to exp(coefficient of A)*exp(coefficient of the interaction term); the simple main effect of B (in terms of an odds ratio) for A = 1 is equal to exp(coefficient of B)*exp(coefficient of the interaction term). Chronic disease pairs significant at p<.10 were studied.

RESULTS

Participants

In total 3,386 participants (52.9% female) completed and returned the self-reported chronic disease questionnaire and the SUQASH questionnaire. The average age of respondents was 67.5 years of age (range: 55-95 years). Forty-seven percent of the participants did not suffer from any chronic disease, while 28%, 14%, 7%, 3% and 1% reported having one, two, three, four and five chronic diseases, respectively. (Table 1).

Table 1. Participant characteristics

Characteristic[a]	Participants (N= 3,386)
Age (years)	67.5 ± 8.3
Sex (N, % female)	1791 (52.9)
Height (cm)	170.0 ± 8.8
Body weight (kg)	75.1 ± 13.8
Chronic respiratory disease	321 (9.5)
Cardiovascular disease	299 (8.8)
Severe bowel disease	112 (3.3)
Liver disease	16 (0.5)
Severe kidney disease	48 (1.4)
Diabetes mellitus	230 (6.8)
Cancer	77 (2.3)
Epilepsy	20 (0.6)
Migraine	158 (4.7)
Neurological disorders and stroke	70 (2.1)
Inflammatory joint disease	302 (8.9)
Rheumatoid arthritis	150 (4.4)
Osteoarthritis of knees, hips or hands	780 (23.0)
Severe back problems	517 (15.3)
Persistent injury due to an accident	132 (3.9)

[a]continuous variables are presented as mean ± standard deviation and dichotomous variables as N (%).

Selection of chronic disease pairs

In total 105 possible chronic disease pairs were assembled from the 15 chronic diseases indicated in the self-reported chronic disease questionnaire (Table 2). Fifty-three pairs were excluded because ten or fewer participants suffered from them. The most common chronic disease pair was 'osteoarthritis of knees, hips and hands' and 'severe back problems' (N= 259). Other chronic disease pairs affecting more than one hundred participants were 'inflammatory joint disease' and 'osteoarthritis of knees, hips and hands' (N= 194); 'chronic respiratory disease' and 'osteoarthritis of knees, hips and hands' (N= 114); and 'inflammatory joint disease' and 'severe back problems' (N= 109).

Table 2. Inclusion/exclusion of chronic disease pairs based on the prevalence of each chronic disease pair in 3386 participants

N= Excluded N < 10 N= 52 included disease pairs	Chronic respiratory disease	Cardiovascular disease	Severe bowel disease	Liver disease	Severe kidney disease	Diabetes mellitus	Cancer	Epilepsy	Migraine	Neurological disorders and stroke	Inflammatory joint disease	Rheumatoid arthritis	Osteoarthritis of knees, hips and hands	Severe back problems
Cardiovascular disease	47													
Severe bowel disease	10	6												
Liver disease	3	3	0											
Severe kidney disease	10	6	1	1										
Diabetes mellitus	40	37	5	4	6									
Cancer	12	15	4	2	6	11								
Epilepsy	5	3	0	0	0	4	3							
Migraine	15	14	12	2	2	4	9	3						
Neurological disorders and stroke	10	14	3	0	0	7	2	2	5					
Inflammatory joint disease	40	40	15	8	8	33	11	3	22	12				
Rheumatoid arthritis	24	19	6	3	3	13	5	1	11	8	73			
Osteoarthritis of knees, hips and hands	114	86	30	20	20	73	19	9	61	20	194	87		
Severe back problems	82	64	25	6	6	35	12	8	47	14	109	54	259	
Persistent injury due to an accident	18	18	3	2	2	12	3	1	14	2	17	7	53	42

For each of the 52 chronic disease pairs that were selected for further study, it was tested whether patients having the combination of the two diseases show higher probabilities of non-compliance compared to the other patients. This was the case for four-

teen chronic disease pairs (Table 3). Chronic respiratory disease seemed to co-occur in five of the pairs. Cardiovascular disease, inflammatory joint disease, rheumatoid arthritis and diabetes mellitus were part of four disease pairs. Osteoarthritis of knees, hips and hands emerged in three disease pairs. The four remaining diseases forming part of disease pairs were severe kidney disease, migraine, back problems and persistent injury due to an accident (Table 3).

Table 3. Chronic disease pairs inversely associated with physical activity guideline compliance

Chronic disease pair	N	Chi-square	p-value
Chronic respiratory disease and Cardiovascular disease	47	3.938	0.048
Chronic respiratory disease and Severe kidney disease	10	4.004	0.098
Chronic respiratory disease and Inflammatory joint disease	40	5.714	0.018
Chronic respiratory disease and Rheumatoid arthritis	24	3.729	0.054
Chronic respiratory disease and Severe back problems	82	4.144	0.042
Cardiovascular disease and Diabetes mellitus	37	3.482	0.062
Cardiovascular disease and Inflammatory joint disease	40	4.262	0.040
Cardiovascular disease and Osteoarthritis of knees, hips and hands	86	7.602	0.006
Diabetes mellitus and Rheumatoid arthritis	13	4.953	0.026
Diabetes mellitus and Osteoarthritis of knees, hips and hands	73	6.371	0.012
Diabetes mellitus and Persistent injury due to an accident	12	3.824	0.100
Migraine and Inflammatory joint disease	22	5.568	0.018
Inflammatory joint disease and Rheumatoid arthritis	73	5.206	0.024
Rheumatoid arthritis and Osteoarthritis of knees, hips and hands	87	4.882	0.028

Association between chronic disease pairs and lack of compliance with the physical activity guideline

Above analyses demonstrated that these 14 chronic disease pairs are particularly interesting, because patients suffering from both diseases of these pairs show a higher probability of non-compliance with the physical activity guideline compared to other patients. Therefore, we included these 14 chronic disease pairs in the logistic regression analysis. The results showed that the interaction term of six chronic disease pairs was statistically significant, which means that the effect of the two diseases combined is not additive. Furthermore, in all six cases the odds ratio of the interaction term is larger than one, which means that patients suffering from both diseases of the pair in question have an increased risk for non-compliance with the Dutch physical activity guideline recommendation compared to what one would expect based on the effects of each of the two diseases alone (Table 4).

Patients who have the chronic disease pair chronic respiratory disease and severe back problems have an even higher risk for non-compliance with the Dutch PA guideline recommendation than expected on the effect of the diseases individually. The same was found for the chronic disease pair migraine and inflammatory joint disease. Patients that have both migraine and inflammatory joint disease have an extra risk to show inadequate PA levels. Four other chronic disease pairs were found to be particularly associated with non-compliance with the PA guideline at a borderline significance level. Because they might still be relevant for clinical practice we decided to present them, as well. The first chronic disease pair was chronic respiratory disease and severe kidney disease. These patients have an extra risk of a lack of PA guideline compliance. The same applies to patients who suffered from chronic respiratory disease and inflammatory joint disease simultaneously. Patients with the chronic disease pair rheumatoid arthritis and inflammatory joint disease, as well as rheumatoid arthritis and osteoarthritis of the knees, hips and hands also have an additional risk to not show adequate PA behaviour (Table 4).

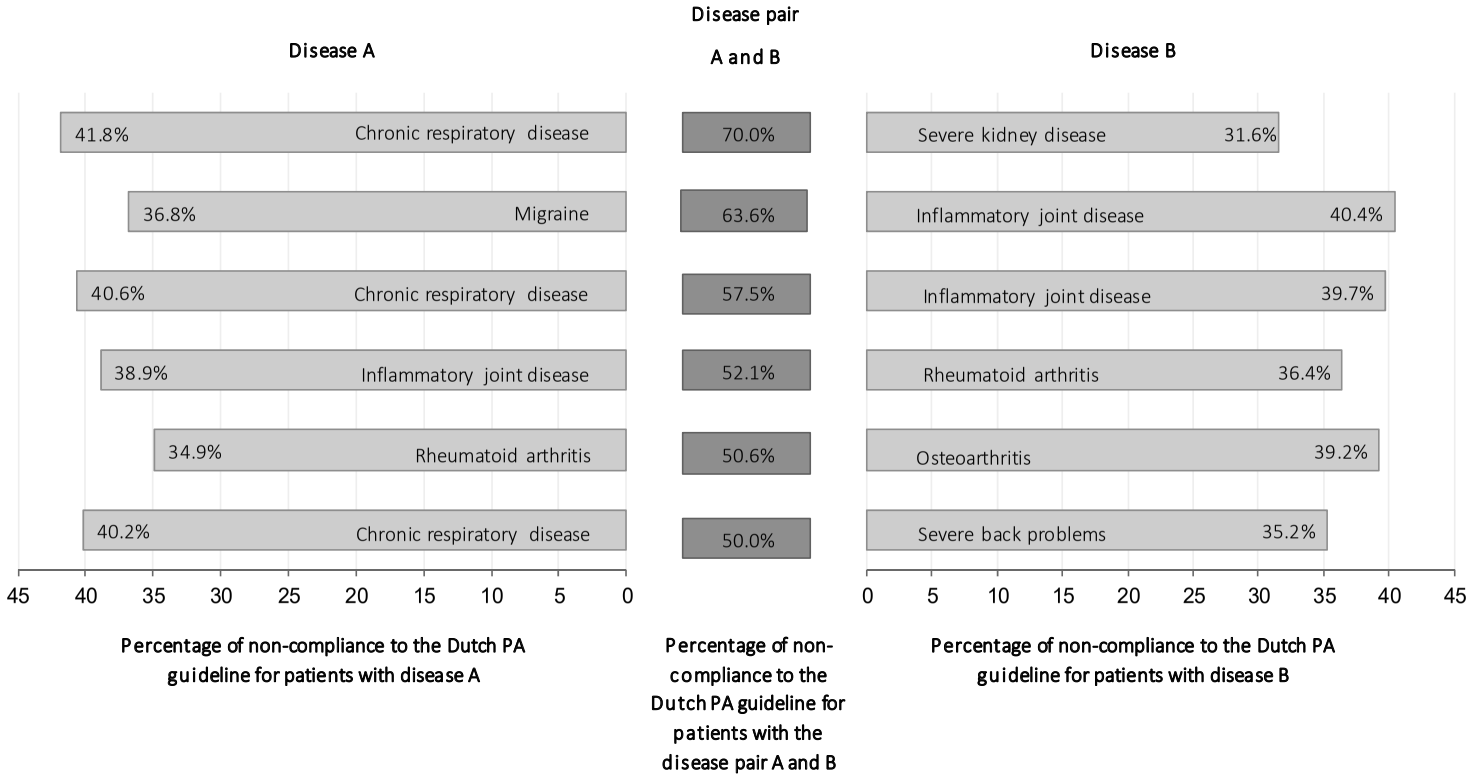
Table 4. Association chronic disease pairs and physical activity guideline compliance

Disease		N	Odds ratio	95% Confidence Interval		p-value
				Lower	Upper	
A	Chronic respiratory disease	274	1.118	0.868	1.439	0.388
B	Cardiovascular disease	252	1.336	1.030	1.731	0.029
A and B	Chronic respiratory disease and cardiovascular disease	47	1.231	0.628	2.413	0.546
A	Chronic respiratory disease	311	1.129	0.891	1.431	0.316
B	Severe kidney disease	38	0.725	0.365	1.443	0.360
A and B	Chronic respiratory disease and severe kidney disease	10	4.478	0.966	20.765	0.055+
A	Chronic respiratory disease	281	1.081	0.842	1.388	0.542
B	Inflammatory joint disease	262	1.042	0.805	1.350	1.042
A and B	Chronic respiratory disease and inflammatory joint disease	40	1.902	0.927	3.902	0.080+
A	Chronic respiratory disease	297	1.120	0.879	1.428	0.358
B	Rheumatoid arthritis	126	1.114	0.775	1.600	0.560
A and B	Chronic respiratory disease and rheumatoid arthritis	24	1.778	0.710	4.454	0.219
A	Chronic respiratory disease	239	1.033	0.788	1.353	0.814
B	Severe back problems	435	0.835	0.675	1.032	0.095
A and B	Chronic respiratory disease and severe back problems	82	1.784	1.033	3.083	0.038*
A	Cardiovascular disease	262	1.379	1.069	1.779	0.013
B	Diabetes mellitus	193	1.710	1.277	2.290	0.000
A and B	Cardiovascular disease and diabetes mellitus	37	0.827	0.391	1.750	0.619
A	Cardiovascular disease	259	1.327	1.027	1.715	0.030
B	Inflammatory joint disease	262	1.077	0.832	1.395	0.572
A and B	Cardiovascular disease and inflammatory joint disease	40	1.377	0.672	2.821	0.382
A	Cardiovascular disease	213	1.247	0.940	1.656	0.126
B	Osteoarthritis of knees, hips and hands	694	1.025	0.862	1.219	0.780
A and B	Cardiovascular disease and osteoarthritis of knees, hips and hands	86	1.448	0.850	2.464	0.173

Disease		N	Odds ratio	95% Confidence Interval		p-value
				Lower	Upper	
A	Diabetes mellitus	217	1.638	1.243	2.159	0.000
B	Rheumatoid arthritis	137	1.156	0.817	1.637	0.413
A and B	Diabetes mellitus and Rheumatoid arthritis	13	1.928	0.549	6.773	0.306
A	Diabetes mellitus	157	1.651	1.195	2.282	0.002
B	Osteoarthritis of knees, hips and hands	707	1.050	0.885	1.247	0.575
A and B	Diabetes mellitus and osteoarthritis of knees, hips and hands	73	1.078	0.602	1.930	0.800
A	Diabetes mellitus	218	1.647	1.251	2.169	0.000
B	Persistent injury due to an accident	120	1.078	0.743	1.565	0.692
A and B	Diabetes mellitus and persistent injury due to an accident	12	1.821	0.504	6.580	0.360
A	Migraine	136	0.910	0.637	1.300	0.605
B	Inflammatory joint disease	280	1.059	0.825	1.360	0.651
A and B	Migraine and inflammatory joint disease	22	2.841	1.078	7.486	0.035*
A	Inflammatory joint disease	229	0.997	0.757	1.313	0.981
B	Rheumatoid arthritis	77	0.896	0.560	1.434	0.647
A and B	Inflammatory joint disease and rheumatoid arthritis	73	1.906	0.938	3.873	0.074+
A	Rheumatoid arthritis	63	0.845	0.500	1.426	0.527
B	Osteoarthritis of knees, hips and hands	693	1.017	0.856	1.208	0.849
A and B	Rheumatoid arthritis and osteoarthritis of knees, hips and hands	87	1.875	0.942	3.735	0.074+

*p≤0.005; +p≤0.01

Figure 2 presents the percentage of participants with disease A, disease B and the chronic disease pair A and B for whom the probability of non-compliance with the Dutch physical activity guideline is larger than compared to what one would expect from the effects of each of the two diseases alone. Each disease pair consists of a disease A and a disease B. The left and the right side of figure 1 present the percentage of non-compliance with the Dutch physical activity guideline for patients that suffered from disease A only, but not from disease B (left side) and for patients that suffered from disease B, but not from disease A (right side). For example, of the patients who had diabetes mellitus, but not rheumatoid arthritis 34.9% did not comply with the Dutch physical activity guideline (Disease A, left side). Of the patients who suffered from rheumatoid arthritis, but not diabetes mellitus, 39.2% did not comply with the Dutch physical activity guideline recommendation (Disease B, right side). Of all patients who suffered from the chronic disease pair diabetes mellitus and rheumatoid arthritis (Disease pair A+B, middle), 69.2% did not comply with the Dutch physical activity guideline. The strongest association of guideline non-compliance was found in patients with the disease pair diabetes mellitus and rheumatoid arthritis (Percentage of noncompliance: 69.2%; Odds ratio: 3.652).



PA = Physical Activity

Figure 2. Percentage of participants with disease A, disease B and/or the disease pair A and B who did not comply with the Dutch physical activity guideline

DISCUSSION

Six chronic disease pairs were shown to be particularly interesting, because patients suffering from both diseases belonging to these disease pairs in question show a higher probability of non-compliance with the Dutch physical activity guideline, compared to what one would expect based on the effects of each of the two diseases alone. These six chronic disease pairs were: chronic respiratory disease and severe back problems; migraine and inflammatory joint disease; chronic respiratory disease and severe kidney disease; chronic respiratory disease and inflammatory joint disease; inflammatory joint disease and rheumatoid arthritis; and rheumatoid arthritis and osteoarthritis of the knees, hips and hands.

Some limitations are worth mentioning. First, the presence or absence of chronic diseases was measured via self-reported questionnaires. In the SMILE cohort study, information on chronic diseases was also registered in EMRs, however not all participants gave written consent to allow comparing self-reported information with data registered in the EMRs by general practitioners. Nevertheless, previous research compared self-reported SMILE cohort data with EMR information and revealed an agreement of over 80% for most of the chronic diseases. This supports the use of self-reported data to answer our research question [18]. Secondly, to preserve as much information as possible, missing values in the self-reported chronic disease questionnaire were interpreted as 'absence of disease'. This may have led to an underestimation of the total disease burden of the population. Thirdly, the self-reported chronic disease questionnaire provided information on fifteen chronic diseases without severity assessment, which could be interpreted as a limitation. Lastly, self-reported PA measurement could have been influenced by social desirability and seasonal factors. Previous research conducted by Sallis et al. [19] already showed that people tend to overestimate their PA. To limit this type of bias, participants were explicitly informed that neither researchers nor their caregivers would receive any information from the self-reported questionnaires.

An exceeded inverse association between the chronic disease pair chronic respiratory disease and severe back problems and Dutch PA guideline compliance was revealed. This chronic disease pair might extra interfere with PA due to the interrelated anatomical and physiological cohesive structure of the thoracic cage, which is formed by the spine, rib cage and associated muscles, which are affected in myriad ways in patients with chronic respiratory disease and severe back problems [20]. One of the main symptoms of chronic respiratory disease, which was defined in the self-reported disease questionnaire as chronic bronchitis, emphysema and asthma, is a hacking cough which may induce and aggravate severe musculoskeletal back pain. Furthermore, biochemical and neurological interactions between chronic respiratory disease and severe back problems might underpin the exceeded inverse association between this chronic dis-

ease pair and inadequate PA levels. A decrease in CO_2 together with an increase in pH inhibit the transfer from haemoglobin of oxygen to tissue cells, which affects normal muscular function, motor control and pain perception [20]. Taken together, the strength of the interdependency between chronic respiratory disease and severe back problems might worsen the pain and decrease functional ability of patients and thereby extra interfere with adequate PA behaviour.

Patients suffering from the chronic disease pair migraine and inflammatory joint disease also showed extraordinary inadequate PA levels. Previous research has shown that the association between migraine and PA is two-sided. On the one hand, PA has been shown to have a beneficial effect on the frequency, intensity and duration of migraine attacks and patient well-being [21-23]. On the other hand, PA has been shown to be a common trigger for headaches and migraine attacks [26, 27]. Strenuous activities often cause dehydration, higher body temperature, low blood sugar and therefore trigger migraine due to low blood oxygen levels [26]. Patients with inflammatory joint disease experience persistent joint pain and swelling of the joints due to the inflammatory process, which can also occur during PA [28]. Being more vigorous, strengthening exercises are often recommended for patients with inflammatory joint disease because they are designed to increase muscle strength. As the muscle becomes stronger, it provides greater joint support and thereby reduces stress and loading on the painful joint. Moreover, strong muscles contribute to better functioning. Therefore, patients that have both migraine and inflammatory joint disease may display particularly inadequate PA levels, because they try to avoid exercises that could trigger a migraine. When stiffness, painful joints and headaches are already bogging patients down, the prospect of PA may seem overwhelming and painful, causing them to limit their activity.

At the 10% significance level it was found that the association between the chronic disease pair chronic respiratory disease and severe kidney disease with PA was exceedingly reversed. Severe kidney disease generally refers to the progressive and irreversible loss of kidney function, in which in the most severe stage renal replacement therapy in the form of either dialysis or kidney transplantation becomes necessary in order to keep the patient alive and maintain quality of life [29]. Physical activity levels in patients with severe kidney disease are usually low [30, 31]. Additionally, these patients report lower physical functioning and performance than those with normal kidney function [30]. Literature has shown that the burden of other chronic diseases in patients with more severe kidney disease is significantly higher [32]. Patients with the disease combination chronic respiratory disease and severe kidney disease may perceive themselves unable to participate in PA because of the disruptive and burdensome effect of both diseases on their daily life and well-being. Moreover, shortness of breath caused by chronic respiratory disease may worsen due to the additional influence of severe kidney disease. The extra fluid in the body can accumulate in the lungs. In addition, anaemia may lead

to oxygen starvation and shortness of breath. The combination of both diseases may also aggravate fatigue. Fatigue, defined as the perception of mental or physical exhaustion is a common symptom in chronic respiratory diseases [33]. As the kidney's fail, they produce less erythropoietin, a hormone that initiates the production of oxygen-carrying blood cells. Consequently, chronic respiratory disease in combination with fewer red blood cells carrying oxygen due to kidney failure leads to anaemia, which causes the muscles and brain to become exhausted very easily [32]. Besides, the physiological explanation for low PA levels in patients who suffer from respiratory disease and severe kidney disease must acknowledge the low statistical power of the analysis of this chronic disease pair (N=10).

Moreover, patients with the chronic disease pair chronic respiratory disease and inflammatory joint disease combined showed extra inadequate PA levels. Previous research showed that joint inflammation might be interrelated with chronic respiratory disease [33]. Long-term inflammation may cause scarring of the lungs, which in turn leads to shortness of breath, chronic dry cough and fatigue. Additionally, inflammation can also cause pleural inflammation, resulting in shortness of breath and painful respiration. The connectedness of both chronic diseases might increase symptom severity, especially pain perception and breathing problems which may in turn explain why patients with chronic respiratory disease and inflammatory joint disease avoid PA and are therefore eminently non-compliant with the Dutch PA guideline recommendation.

Last, two chronic disease pairs that show an ancillary inverse association with PA are rheumatoid arthritis and inflammatory joint disease and rheumatoid arthritis and osteoarthritis of the knees, hips and hands. A phenomenological study conducted by Petursdottir et al. [34] identified facilitators and barriers to exercising among people with osteoarthritis. Patients suffering from osteoarthritis of the knees, hips and hands often have difficulties with PA because of symptoms such as pain and stiffness. Furthermore, uncertainty about the amount and type of exercise they require, as well as when to expect benefits, seem to contribute to inadequate PA levels [34]. Prior negative experiences with overtraining resulting in increased pain levels after PA have been found in 15% of all patients with osteoarthritis and might contribute to PA guideline non-compliance [34]. Furthermore, it is well know that the pain levels of all individual diseases vary from day to day. The combination of two diseases might cause constant pain, which the patient may perceive as too intense to engage in PA. Moreover, perceived frailty and perceived poor health might play a role in patients with one of these two chronic disease pairs [35].

CONCLUSIONS

Six chronic disease pairs were identified in which having the combination of the two diseases leads to even more non-compliance than expected based on the sum of the diseases individually: chronic respiratory disease and severe back problems; migraine and inflammatory joint disease; chronic respiratory disease and severe kidney disease; chronic respiratory disease and inflammatory joint disease; inflammatory joint disease and rheumatoid arthritis; and rheumatoid arthritis and osteoarthritis of the knees, hips and hands. The results of the present study may alert health care professionals of particularly low physical activity levels in patients with one of the six chronic disease pairs. Further research is needed to back up our findings to test whether these results remain stable in different patient populations.

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APPENDIX

APPENDIX 1. CHRONIC DISEASE PAIRS

Table 1: All possible chronic disease pairs (*N*=105)

No.	Chronic disease pair
1	Chronic respiratory disease and Cardiovascular disease
2	Chronic respiratory disease and Severe bowel disease
3*	Chronic respiratory disease and Liver disease
4	Chronic respiratory disease and Severe kidney disease
5	Chronic respiratory disease and Diabetes mellitus
6	Chronic respiratory disease and Caner
7*	Chronic respiratory disease and Epilepsy
8	Chronic respiratory disease and Migraine
9	Chronic respiratory disease and Neurological disorders and stroke
10	Chronic respiratory disease and Inflammatory joint disease
11	Chronic respiratory disease and Rheumatoid arthritis
12	Chronic respiratory disease and Osteoarthritis of knees, hips and hands
13	Chronic respiratory disease and Severe back problems
14	Chronic respiratory disease and Persistent injury due to an accident
15*	Cardiovascular disease and Severe bowel disease
16*	Cardiovascular disease and Liver disease
17*	Cardiovascular disease and Severe kidney disease
18	Cardiovascular disease and Diabetes mellitus
19	Cardiovascular disease and Cancer
20*	Cardiovascular disease and Epilepsy
21	Cardiovascular disease and Migraine
22	Cardiovascular disease and Neurological disorders and stroke
23	Cardiovascular disease and Inflammatory joint disease
24	Cardiovascular disease and Rheumatoid arthritis
25	Cardiovascular disease and Osteoarthritis of knees, hips and hands
26	Cardiovascular disease and Severe back problems
27	Cardiovascular disease and Persistent injury due to an accident
28*	Severe bowel disease and Liver disease
29*	Severe bowel disease and Severe kidney disease
30*	Severe bowel disease and Diabetes mellitus
31*	Severe bowel disease and Cancer
32*	Severe bowel disease and Epilepsy
33	Severe bowel disease and Migraine
34*	Severe bowel disease and Neurological disorders and stroke

No.	Chronic disease pair
35	Severe bowel disease and Inflammatory joint disease
36*	Severe bowel disease and Rheumatoid arthritis
37	Severe bowel disease and Osteoarthritis of knees, hips and hands
38	Severe bowel disease and Severe back problems
39*	Severe bowel disease and Persistent injury due to an accident
40*	Liver disease and Severe kidney disease
41*	Liver disease and Diabetes mellitus
42*	Liver disease and Cancer
43*	Liver disease and Epilepsy
44*	Liver disease and Migraine
45*	Liver disease and Neurological disorders and stroke
46*	Liver disease and Inflammatory joint disease
47*	Liver disease and Rheumatoid arthritis
48*	Liver disease and Osteoarthritis of knees, hips and hands
49*	Liver disease and Severe back problems
50*	Liver disease and Persistent injury due to an accident
51*	Severe kidney disease and Diabetes mellitus
52*	Severe kidney disease and Cancer
53*	Severe kidney disease and Epilepsy
54*	Severe kidney disease and Migraine
55*	Severe kidney disease and Neurological disorders and stroke
56*	Severe kidney disease and Inflammatory joint disease
57*	Severe kidney disease and Rheumatoid arthritis
58	Severe kidney disease and Osteoarthritis of knees, hips and hands
59*	Severe kidney disease and Severe back problems
60*	Severe kidney disease and Persistent injury due to an accident
61	Diabetes mellitus and Cancer
62*	Diabetes mellitus and Epilepsy
63*	Diabetes mellitus and Migraine
64*	Diabetes mellitus and Neurological disorders and stroke
65	Diabetes mellitus and Inflammatory joint disease
66	Diabetes mellitus and Rheumatoid arthritis
67	Diabetes mellitus and Osteoarthritis of knees, hips and hands
68	Diabetes mellitus and Severe back problems
69	Diabetes mellitus and Persistent injury due to an accident
70*	Cancer and Epilepsy
71*	Cancer and Migraine
72*	Cancer and Neurological disorders and stroke
73	Cancer and Inflammatory joint disease

No.	Chronic disease pair
74*	Cancer and Rheumatoid arthritis
75	Cancer and Osteoarthritis of knees, hips and hands
76	Cancer and Severe back problems
77*	Cancer and Persistent injury due to an accident
78*	Epilepsy and Migraine
79*	Epilepsy and Neurological disorders and stroke
80*	Epilepsy and Inflammatory joint disease
81*	Epilepsy and Rheumatoid arthritis
82*	Epilepsy and Osteoarthritis of knees, hips and hands
83*	Epilepsy and Severe back problems
84*	Epilepsy and Persistent injury due to an accident
85*	Migraine and Neurological disorders and stroke
86	Migraine and Inflammatory joint disease
87	Migraine and Rheumatoid arthritis
88	Migraine and Osteoarthritis of knees, hips and hands
89	Migraine and Severe back problems
90	Migraine and Persistent injury due to an accident
91	Neurological disorders and stroke and Inflammatory joint disease
92*	Neurological disorders and stroke and Rheumatoid arthritis
93	Neurological disorders and stroke and Osteoarthritis of knees, hips and hands
94	Neurological disorders and stroke and Severe back problems
95*	Neurological disorders and stroke and Persistent injury due to an accident
96	Inflammatory joint disease and Rheumatoid arthritis
97	Inflammatory joint disease and Osteoarthritis of knees, hips and hands
98	Inflammatory joint disease and Severe back problems
99	Inflammatory joint disease and Persistent injury due to an accident
100	Rheumatoid arthritis and Osteoarthritis of knees, hips and hands
101	Rheumatoid arthritis and Severe back problems
102*	Rheumatoid arthritis and Persistent injury due to an accident
103	Osteoarthritis of knees, hips and hands and Severe back problems
104	Osteoarthritis of knees, hips and hands and Persistent injury due to an accident
105	Severe back problems and Persistent injury due to an accident

*DUOs excluded from our analysis because N≤10

Chapter 8

Using Latent Profile Analysis to Develop Multimorbidity - Physical Activity Behaviour Profiles:

results from the SMILE cohort study

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ABSTRACT

Objective:
To model physical activity behaviour for specific types of physical activity in a representative, general-practice population of older adults with multimorbidity.

Design:
Latent profile analysis was conducted to determine a multimorbidity - physical activity behavior model. Profile classes were compared regarding the presence of fifteen common chronic diseases and seven specific physical activity types.

Setting:
Cross-sectional data from 3,386 patients participating in the 2003 wave of the Dutch cohort study SMILE was used.

Participants:
Patients aged 55 years and over, registered in one of the participating nine primary healthcare centres of the SMILE cohort study who completed both the lifestyle and chronic disease questionnaire were included in our analysis.

Primary and secondary outcome measures:
Number and multimorbidity - physical activity behaviour of latent profile classes.

Results:
The best fit was a 4-class solution with (1) a group with the lowest prevalence of cardiovascular disease, cancer and rheumatoid arthritis, very active in walking, light and intensive household activities; (2) a relatively healthy group in which liver disease or cirrhosis and cycling, gardening, odd jobs and sports were prevalent; (3) a group with the lowest prevalence of migraine, inflammatory joint disease and lowest activity levels in all types of physical activities except for light household chores; and (4) a group with the highest prevalence of all chronic diseases except for liver disease or cirrhosis with moderate physical activity levels.

Conclusions:
Multimorbidity does not seem to be the main obstacle to engaging in physical activity. Although, the pattern of physical activity behaviour for all seven types of activities seemed comparable among classes, there is a difference between the classes with respect to the general level of the probability to execute each type of activity.

INTRODUCTION

The increase of patients with multimorbidity along with the negative consequences of co-occurring chronic diseases has attracted much attention in the primary care literature and is acknowledged as a research priority [1, 2]. The importance of lifestyle factors, such as insufficient physical activity is often highlighted in this research area. Previous studies have demonstrated a negative association of insufficient physical activity with the occurrence of most common chronic diseases such as heart disease, cancer, diabetes mellitus, stroke and obesity [3-9]. Moreover, it has been shown that physical activity is as effective as other non-lifestyle factors in relation to mortality benefits in the secondary prevention of the above mentioned chronic diseases [10]. Owing to the beneficial effects of physical activity in relation to chronic diseases it is important for health care professionals to help individuals to initiate and maintain appropriate physical activity levels. A better understanding about which patients specifically need attention would facilitate more targeted approaches to raising and maintaining appropriate physical activity levels in patients with chronic diseases.

On the population level appropriate physical activity is often measured in terms of compliance with physical activity guideline recommendations which state that in order to stay healthy or to improve health, older adults aged 55 years and over should carry out at least 30 minutes of moderate to intense physical activity (3 to 5 METs) at least five days per week [11]. However, to achieve behavioural change, research needs to focus on particular physical activity behaviours [12]. In this respect, leisure-time physical activity is the activity that patients choose to do in their free time. People engage in different behaviours in their free time, such as walking, cycling, gardening, odd jobs, household activities and sports. If the goal is to carry out interventions for patients with multimorbidity, the role of multimorbidity should be investigated in relation to a particular behaviour. We are not aware, however, of any study reporting on the association between multimorbidity and different physical activity types.

The objective of our study was to describe the association between multimorbidity and leisure-time physical activity types. To this end, we performed latent profile analysis, by examining chronic disease variables and leisure-time physical activity variables simultaneously in order to determine multimorbidity - physical activity behaviour typologies existing within our data. We hypothesize that complex chronic disease patterns exist within this large general practice population and that these meaningful patterns may encompass a range of physical activity behaviours. Therefore, we sought to identify the underlying patterns (or classes) of chronic diseases and physical activity lifestyle based on responses to fifteen chronic diseases and seven physical activity types.

We used latent profile analysis and not standard cluster analysis, because latent profile analysis allowed us to deal with mixed measurement levels (different scaling types) of our variables. Multimorbidity was measured binary and physical activity behaviour was measured continuous in the SMILE cohort. This study was innovative in the area of multimorbidity research because (1) information on fifteen common chronic diseases and seven different physical activity types were entered simultaneously into a latent profile model to determine multimorbidity - physical activity behaviour profiles and (2) we modelled physical activity behaviour for seven specific types of physical activity i.e. walking, cycling, gardening activities, odd jobs, light household chores, intense household activities and sports. One of the greatest obstacles in the ongoing development of physical activity interventions for patients with multimorbidity is the lack of data on leisure-time physical activity. The aim of the present study was to address this gap and to describe the types of physical activity performed in a representative, population-based Dutch sample of older adults with multimorbidity.

METHOD

Study design and setting

For the present cross-sectional study, data from the dynamic prospective cohort study SMILE, the *S*tudy of *M*edical *I*nformation and *L*ifestyles in *E*indhoven were used. The SMILE study, a joint initiative between Maastricht University and the Eindhoven Cooperation of Primary Health Care Centres (SGE) including 32 general practitioners representing nine primary health care centres was conducted between 2002 and 2010. Data on morbidity, mortality, medication intake and health care consultations were registered in the electronic medical records (EMRs) of all nine primary health care centres. Patients were asked questions about lifestyle and chronic diseases in self-administered, paper-based, annual questionnaires. The SMILE study has been approved by the medical ethics committee of the Maastricht academic hospital (MEC 07-4-030) and detailed information about the study protocol was published previously [13]. To enhance transparency and reproducibility, this article has been written according to the STROBE checklist for cohort studies.

Participants

All patients aged 12 years and over, registered in one of the participating nine primary healthcare centres were invited to participate in the SMILE study. For the present study, only data from patients aged 55 years and older were used. Since the SMILE cohort data collected in 2003 on chronic diseases and physical activity came from largest number of patients, data from that year were used for the present analyses.

Variables

The variables included fifteen self-reported chronic diseases and seven types of leisure time physical activity, all of which were scored binary (i.e. presence versus absence; participation versus lack of participation). Dichotomous variable specifications were selected for the final presentation to enhance the interpretability of findings. Specific model estimates were tested for physical activity measured continuously (minutes per day), twice for physical activity measured categorical (once categories were made based on recommendations from current literature and once by data binning) and binary. Since we found comparable results, we chose to present the most understandable model.

Chronic respiratory disease, cardiovascular disease, severe bowel disease, liver disease or cirrhosis, severe kidney disease, diabetes mellitus, cancer, epilepsy, migraine, neurological disorders and stroke, inflammatory joint disease, rheumatoid arthritis, osteoarthritis of knees, hips and hands, severe back problems, and persistent injury from an accident occurring at home, in sports, school/work or traffic were the fifteen self-reported chronic diseases included in the analysis. Types of leisure-time physical activity included: walking, cycling, gardening, odd jobs, light and intense household activities and sports.

Bias

The chronic disease questionnaire had a dichotomous structure (yes/no) and patients were asked to mark (thick 'yes') for all diseases they currently have. We hypothesize that most patients followed this instruction and only indicated the presence of each disease without explicitly stating the absence (by thicking 'no') of all other diseases listed. This has led to missing values ranging from 17.5% to 24.2%. In order to correct for the indistinct instruction, we interpreted all missing values for the fifteen chronic diseases as 'disease being absent'. In addition, we performed sensitivity analysis and found comparable results for patients with and without missing data on the chronic disease variables.

Data sources/measurement

All patients aged 55 years and over who returned both the lifestyle (November 2003) and chronic disease questionnaires (May 2003) were included in the analysis.

Self-reported chronic disease questionnaire
The self-reported chronic disease questionnaire measured the presence or absence of fifteen chronic diseases and was based on a medical screening questionnaire of the

Dutch Association of General Practitioners (LHV) [13, 14]. At the end of the questionnaire an open question was asked that allowed all patients to report diseases from which they currently suffered, but that were not included in the fifteen chronic diseases listed. All chronic diseases listed under this open question (N= 1,077) were assigned to the existing categories of the questionnaire to maximise the usefulness of the available data. Two researchers (SD and IM) and a medical specialist (JT) independently assigned each disease to the categories.

Short Questionnaire to Assess Health-enhancing physical activity (SQUASH)

The *S*hort *Qu*estionnaire to *A*ssess *H*ealth-enhancing physical activity (SQUASH) was used to measure physical activity behaviour. The SQUASH questionnaire asks participants about the number of days they were active per week, the average time per day they were active and the intensity of the physical activity they performed. In the SQUASH questionnaire physical activity is pre-structured in (a) commuting activities, (b) leisure-time activities, (c) household activities and (d) activities at work and school. Examples are provided for all four categories. A Metabolic Equivalent (MET value), defined as the ratio of the work metabolic rate to the resting metabolic rate according to the Ainsworth compendium for physical activity is assigned to each type of physical activity [15]. Activities with a MET value between 1.6 and 2.9 were classified as intense; activities with a MET value between 3.0 and 5.9 were qualified as moderate-intense and physical activities with ≥ 6 METs were referred to as vigorous-intense [15, 16]. Hobbies were excluded from this questionnaire because they often have low MET values (~2 MET), however hobbies that did have meaningful MET values were noted under sports. The data used for the present article did not include information about activities at work and school, because the population was 55 years and over and the majority of these patients were no longer working. By multiplying the frequency (days per week) and duration (minutes per day), the total number minutes spent on each activity were calculated. Previous research showed the SQUASH questionnaire to be a reliable and sound questionnaire for measuring physical activity among the Dutch adult population [16].

Statistical analysis

This study aimed to identify the pattern of co-occurrence of fifteen common chronic diseases and seven physical activity types in the Dutch general practice population. Latent profile analysis was used to identify groups of related diseases and physical activity types (i.e. latent profile classes). Latent profile analysis classifies individuals according to their distribution on all chronic diseases and physical activity types [17, 18]. To determine which model best explained the latent association between chronic diseases and physical activity behaviour, the relative goodness of fit estimates Akaike's information criterion (AIC), the Bayesian information criterion (BIC), the adjusted Bayesian

information criterion (SSA-BIC) and the entropy value were jointly considered [19-21]. The optimal number of latent profile classes is determined by the model with the lowest AIC, the lowest BIC, the lowest SSA-BIC and the highest entropy value, respectively [21]. In addition to the model fit information provided by MPlus, we calculated the bootstrap -2 loglikelihood-ratio difference test (AIC – 2* number of free parameters). This test compares the model with K classes to a model with (K-1) classes. Because there are no criteria which are commonly accepted as the best for determining the number of classes, we also considered latent profile model interpretability to determine the most optimal model. A series of latent profile analysis with two- to five classes per model were executed.

According to the response probabilities of all 22 variables for each individual (presence of 15 chronic diseases and performance on 7 specific physical activity types) individuals were allocated to the latent profile class for which they had the highest posterior probability. For each patient the posterior probability of belonging to each latent profile class is calculated by the statistical software package, based on the model estimates. Subsequently, patients were allocated to the class for which this probability is the greatest. Item response probabilities were used to characterise latent profile classes in a similar way to the use of factor loadings in factor analysis. Latent profile analysis was performed using Mplus version 7 statistical software (Los Angeles, CA: Muthén and Muthén. Seventh Edition) [22].

RESULTS

Participants

In total 3,386 patients returned both the lifestyle and chronic disease questionnaire. Fifty-three percent of the patients were female and the average age was 68 (SD: 8.3) years. The most prevalent chronic diseases were ‘osteoarthritis of the knees, hips and hands’ (23%), ‘severe back problems, hernia, sciatica or osteoarthritis’ (15%) and ‘chronic bronchitis, emphysema and asthma’ (10%).

LATENT PROFILE ANALYSIS

Number of classes

To obtain an overall picture about latent profile classes of chronic diseases and physical activity, we examined the two- to five class models. Statistically, the four-class and five-class solutions seemed to provide the best fitting models (Table 1).

Table 1. Latent profile class models and relative goodness of fit indices.

Latent profile class model	-2 Log-likelihood	Number of parameters	AIC	BIC	SSA-BIC	Entropy
2 classes	50407.614	45	50497.614	50773.347	50630.361	0.681
3 classes	49725.626	68	49861.626	50278.289	50062.222	0.709
4 classes	49490.131	91	49672.131	50229.724	49940.575	0.763
5 classes	49277.266	114	49505.266	50203.790	49841.559	0.740

AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; SSA-BIC, Sample-Size Adjusted BIC

When comparing the latent profile four-class model with the latent profile five-class model an increase in the number of parameters from 91 to 114 was found and AIC, BIC and adjusted BIC values were slightly lower (AIC_{4class}: 49672.131 versus AIC_{5class}: 49505.266; BIC_{4class}: 50229.724 versus BIC_{5class}: 50203.790; $SAA\text{-}BIC_{4class}$: 49940.575 versus $SSA\text{-}BIC_{5class}$: 49841.559). Entropy results were highest for the four-class model. In addition to the model fit information provided by MPlus, we calculated the bootstrap -2 loglikelihood-ratio difference test and compared the model with k classes (in our case 5) to the model with (k-1) classes (in our case, 5 - 1 = 4). The result of the -2 likelihood-ratio test showed a significant difference ($p<0.005$; -2 Log-likelihood ratio: 212.865; $\chi^{2(df:23;0.995)}$: 44.181). When examining the latent profile two- to five-class models from a content perspective, we found that in the four- and five-class model, the distinction between classes for the musculoskeletal disorders became clearly visible (Figure 1). However, the five-class model did not add much information to the four-class model: (1) the pattern across all seven physical activity types was comparable in the four and five class model, thus the five class model did not add new information; (2) the magnitude of the probability of executing each types of activity differed among profile classes was also comparable between both models; (3) the relatively healthy group showed the highest levels on 'more intense' physical activity types like cycling, gardening, intense household activities and sports (this was also comparable between both models) and (4) in both models light household activities were performed most. Summarized, the main results were the same and only slight differences were found in the probability of chronic diseases between the four and five class model. From a statistical point of view, the difference in AIC and SSA-BIC was hardly worth mentioning; the number of parameters increased indicating an extra complex model and the four-class model had even higher entropy. Ultimately, the four-class model was chosen for thorough investigation.

Classification of participants based on their most likely latent class membership

For all 3,386 participants MPlus estimated the probability that the person belonged to the first, second, third or fourth profile class. For example, for patient 1 there was a 90% probability that the person belonged to the first class, a 1% probability of belong-

ing to the second class, 0% of belonging to the third class and 8.9% of being a member of the fourth class. Thus, for patient 1 MPlus decided that he or she belonged to the first class since the probability associated to that class was the largest. Based on this rule, MPlus categorised all 3,386 patients into one of four none overlapping classes. The results showed that out of the 3,386 patients (100%), 1612 (47.6%) were members of latent profile class 1, 327 (9.7%) were part of latent profile class 2, 1081 (31.9%) belonged to latent profile class 3 and 366 (10.8%) were part of latent profile class 4. No difference in age and gender distribution was found between the four classes.

Latent profile classes

The proportion of participants assigned to each of the four latent profile classes and the probabilities for each chronic disease and physical activity type by profile are presented in Table 2. The probabilities listed for each chronic disease and physical activity type are parameter estimates and can be interpreted as the percentage of patients within the given latent profile class who reported having the relevant chronic disease respectively perform the physical activity type in question. For example, consider the question 'Do you have chronic respiratory disease'? The probability of answering 'yes' to this question was 7.0% for the first profile class, 6.4% for the second profile class, 9.7% for the third profile class and 20.9% for the fourth profile class. Consequently, the chance of answering 'no' to this question was 93% for the first profile class, 93.6% for the second profile class, 90.3% for the third profile class and 79.1% for the fourth profile class. The same applied to physical activity behaviour, since we present it binary. The probability reflects the percentage of participants within the given latent profile class who performed the given physical activity type. For example, the chance of walking was 76.6% for the patients in profile class 1. Conversely 23.4% of the patients in profile class 1 did not walk. Looking at the pattern of estimated percentages for all fifteen chronic disease variables and seven physical activity types is necessary in order to characterize each class. A graph of chronic diseases and physical activity type probabilities for all four latent profiles is presented in Figure 1.

Latent profile class 1

Latent profile 1 class consisted of patients with the lowest chance of cardiovascular disease, cancer and rheumatoid arthritis combined with the highest probabilities for walking and light and intensive household activities compared to the three other latent class profiles. Most patients were classified as members of latent profile class 1 (n=1612) and the probabilities for cardiovascular disease, cancer and rheumatoid arthritis were 6.8%, 1.8% and 1.2%, respectively. The chance of having one of these three diseases was lower in latent profile class 1 compared with the total population of 3,386 patients (where these values were 8.8%, 2.3% and 4.4%, respectively). With respect to the physical activity types, the probabilities for walking, light household chores and

intense household activities were 76.6%, 98.0% and 56.7%, respectively. Compared to the overall population the probabilities for walking, light and intensive household chores were 20.2%, 28.6% and 22.3% higher, respectively.

Latent profile class 2

Compared to the other three latent profile classes, class two was generally the healthiest group with the highest probabilities for liver disease or cirrhosis, cycling, gardening, odd jobs and sport. The probabilities for chronic respiratory disease (6,4%), severe bowel disease (2.0%), severe kidney disease (0.6%), diabetes mellitus (4.7%), epilepsy (0%), neurological disorders and stroke (1.4%), osteoarthritis of the knees, hips and hands (12.1%) and persistent injury from an accident (2.3%) were lowest among the four profile classes. In latent profile class 2, the probability for liver disease or cirrhosis was 0.9% and exceeded not only the probabilities of the other three profile classes, but also those of the total population of 3,386 patients (0.5%). The probabilities for cycling, gardening, odd jobs and sports were also highest of all four profile classes, and higher than those in the total population. In latent profile class 2, which consisted of 327 patients, the chance for cycling was 72.2%, for gardening 67.6%, for odd jobs 59.0% and for sports 55.5%, while these values were 44.4%, 43.9%, 28.3% and 41.2%, respectively for the overall population of 3,386 patients.

Latent profile class 3

Latent profile class 3 consisted of patients with the lowest probability for migraine, inflammatory joint disease and all physical activity types except light household activities. Of the 1081 patients belonging to profile class 4, the probabilities for migraine and inflammatory joint disease were lowest at 2.3% and 3.4%, respectively. Of the total of 3,386 patients more patients reported having migraines and struggling with inflammatory joint disease (4.7% and 8.9%, respectively). The probabilities for walking (21.2%), cycling (6.4%), gardening (12.2%), odd jobs (5.8%), intensive household activities (9.2%) and sports (22.2%) were the lowest of the four profile classes and lower than that of the overall population that reported engaging in these six physical activity types.

Latent profile class 4

The highest probability for all chronic diseases except for liver disease or cirrhosis together with moderate physical activity levels were designated as latent profile class 4. All chronic disease probabilities were higher compared to the other three latent profile classes and, compared to the proportion of patients from the overall population that reported to have one of these 14 chronic diseases, as well. The probabilities for the 366 patients assigned to latent profile class 4 were 20.9% for chronic respiratory disease, 15.2% for cardiovascular disease, 5.1% for severe bowel disease, 2.5% for severe kidney disease, 10.0% for diabetes mellitus, 3.6% for cancer, 2.2% for epilepsy, 11.7% for migraine, 4.3% for neurological disorders and stroke, 47.3% for inflammatory joint disease,

24.5% for rheumatoid arthritis, 83.7% for osteoarthritis of the knees, hips and hands, 55.3% for severe back problems and 10.1% for persistent injury from an accident. Probabilities for all types of physical activity were moderate compared to the other three class profiles. The probability of being able to walk and perform light household activities was higher compared to the proportion of the overall population that reported performing these physical activity types (58.1% versus 56.4% and 78.0% versus 69.4%, respectively). For all other physical activity types, the probability was lower compared to the overall population.

The four latent profile classes were labelled as follows:

Profile class 1. Group with the lowest prevalence of cardiovascular disease, cancer and rheumatoid arthritis and very active in walking, light and intense household activities

Profile class 2. Relatively healthy group with a high prevalence of liver disease or cirrhosis, active in cycling, gardening, odd jobs and sports

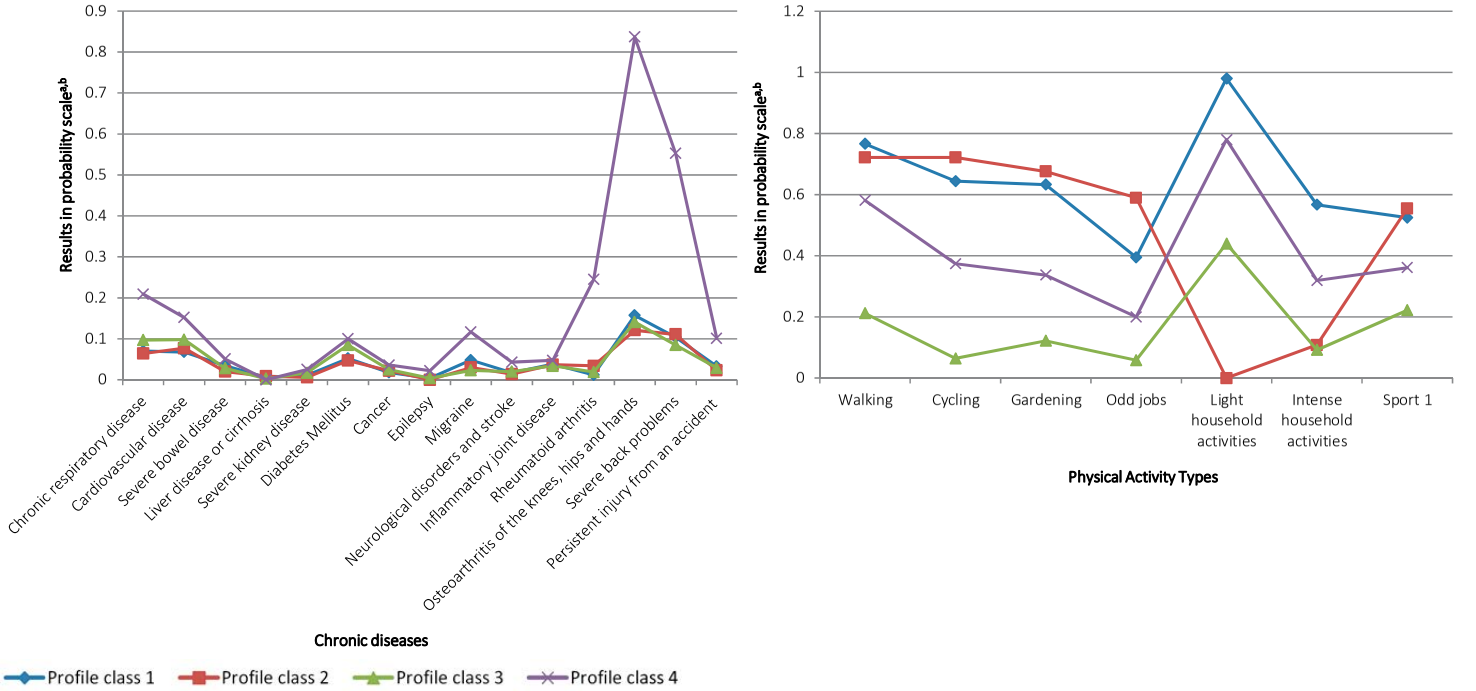
Profile class 3. Group with the lowest prevalence of migraine, inflammatory joint disease and lowest activity levels in all types of physical activities except for light household chores

Profile class 4. Group with the highest prevalence of all chronic diseases except for liver disease or cirrhosis with moderate physical activity levels

Table 2. Latent profile specific probabilities for all chronic diseases and physical activity types.

Variable	Total population (N=3,386) N (%)	Latent profile class 1 (n=1612)	Latent profile class 2 (n=327)	Latent profile class 3 (n=1081)	Latent profile class 4 (n=366)
Chronic diseases					
Chronic respiratory disease	321 (9.5)	0.070	0.064	0.097	0.209[a]
Cardiovascular disease	299 (8.8)	0.068	0.077	0.098	0.152[a]
Severe bowel disease	112 (3.3)	0.034	0.020	0.028	0.051[a]
Liver disease or cirrhosis	16 (0.5)	0.006	0.009[a]	0.003	0.000
Severe kidney disease	48 (1.4)	0.011	0.006	0.017	0.025[a]
Diabetes Mellitus	230 (6.8)	0.052	0.047	0.085	0.100[a]
Cancer	77 (2.3)	0.018	0.022	0.025	0.036[a]
Epilepsy	20 (0.6)	0.004	0.000	0.004	0.022[a]
Migraine	158 (4.7)	0.048	0.030	0.023	0.117[a]
Neurological disorders and stroke	70 (2.1)	0.017	0.014	0.020	0.043[a]
Inflammatory joint disease	302 (8.9)	0.038	0.037	0.034	0.473[a]
Rheumatoid arthritis	150 (4.4)	0.012	0.034	0.019	0.245[a]
Osteoarthritis of the knees, hips and hands	780 (23.0)	0.157	0.121	0.141	0.837[a]
Severe back problems	517 (15.3)	0.104	0.111	0.085	0.553[a]
Persistent injury from an accident	132 (3.9)	0.033	0.023	0.029	0.101[a]
Physical activity types					
Walking	1910 (56.4)	0.766[a]	0.722	0.212	0.581
Cycling	1503 (44.4)	0.664	0.722[a]	0.064	0.374
Gardening	1487 (43.9)	0.633	0.676[a]	0.122	0.337
Odd jobs	957 (28.3)	0.395	0.590[a]	0.058	0.200
Light household activities	2351 (69.4)	0.980[a]	0.000	0.440	0.780
Intense household activities	1165 (34.4)	0.567[a]	0.108	0.092	0.319
Sport 1	1394 (41.2)	0.525	0.555[a]	0.222	0.361

[a] Highest probability for the indicator variable across the four profile classes



[a]This legend applies to both graphs included in Figure 1. The graph was split to enhance visibility of class proportions caused by large differences in the scale of class probabilities (y-axis)

[b]The y-axis represents the probabilities of answering 'yes' to each item given that a person belongs to a certain profile class. So, if a person belongs to profile class 4, he or she has a 20.9% probability of saying 'yes, I have chronic respiratory disease' and thus a 79.1% chance of answering 'no, I do not have chronic respiratory disease'. By contrast, if a patient belongs to class 3, he or she has a 9.7% probability of saying 'yes, I have chronic respiratory disease'.

Figure 1. Chronic disease and physical activity type probabilities for the latent profile four class model.

DISCUSSION

A statement of the principal findings

Latent profile analysis was executed to establish a multimorbidity - physical activity behavior model. Four latent profiles were identified. The first group had the lowest prevalence of cardiovascular disease, cancer, rheumatoid arthritis and engaged the most in walking and household activities. The second group was the healthiest and had the highest prevalence of liver disease or cirrhosis, cycling, gardening, odd jobs and sports. The third group had the lowest prevalence of migraine, inflammatory joint disease and all types of physical activities except light household chores. The fourth group had the highest prevalence of all chronic diseases except for liver disease or cirrhosis and had moderate activity levels.

Strengths and weaknesses of the study

The strengths of our study included the use of latent profile analysis incorporating both chronic diseases and physical activity types simultaneously to obtain in depth information about the association between multimorbidity and physical activity; the availability of information on different types of leisure time physical activity; the rigorous statistical analyses performed; and the large sample size. The main weakness was that the presence or absence of chronic diseases was measured via a self-reported questionnaire. Information on chronic diseases was also registered in an electronic medical record. However, we were unable to compare the data due to issues of informed consent. Nonetheless, correspondence of over 80% for most of the fifteen chronic diseases between self-reported data and electronic medical record data was reported in previous research on the SMILE cohort, which supports the use of self-reports in the present study [23]. The self-reported questionnaire did not provide information about the severity of each chronic disease, either, which could be interpreted as limitation. Aside from that, social desirability might have influenced the self-reported physical activity data, although participants were explicitly informed that none of the information reported in the questionnaires would be enclosed to either the researchers or their caregivers.

Strengths and weaknesses in relation to other studies, discussing important differences in results

Although the use of latent profile analysis to establish clusters of multimorbidity is becoming increasingly common, latent profile analysis has to our knowledge never before been used in the area of multimorbidity research [24-26]. The present study was the first to include both chronic disease variables and physical activity variables simultane-

ously in one latent profile model. Moreover, to our knowledge, we were also the first to assess physical activity behaviour among seven different types of physical activity in relation to multimorbidity. For that reason we are unable to compare our findings to previous research. Instead, we did additional analysis to check the robustness of our findings. First, we performed a sensitivity analysis of the sports variable. In the SQUASH questionnaire patients could opt to report up to four sports activities in response to an open question. For each sports activity they were asked to indicate on how many days per week they performed the activity and how much time on average they engaged in each sport. Our data showed that most older adults only perform one sports activity. Since, less than 10% reported doing more than two sports regularly, we performed the latent profile analysis twice: first, we included all four sports variables in the model; second, we only included the first sports activity listed in our model. The results showed comparable latent profile classes. Nonetheless, we decided to only include the primary (first) sports activity in our final model to 1) enhance stability among the four latent profile classes and 2) to acknowledge and accurately reflect in the profiles identified that the majority of older adults performs only one sports activity regularly.

Second, we conducted the latent profile analysis three times. The fifteen chronic disease variables were included in all three models but we diversified the measurement types for the seven physical activity types (binary; ordinal; and continuous). The results showed identical latent profile classes. Since the results were the same, we chose to present the binary physical activity measurement for the sake of simplicity and clarity.

Possible explanations and implications for clinicians and policymakers based on this study

First, the results of our study suggest that chronic diseases may not be the main obstacle to physical activity, since the highest probability of most chronic diseases was linked to moderate probabilities of physical inactivity. Previous research on motives and barriers to physical activity among older adults with limitations showed that almost half of those with severe or moderate limitations reported disease management and health maintenance as a motive to be physically active [27]. We hypothesize that a higher probability for chronic diseases and/or multimorbidity is related to a higher probability of obtaining physical activity advice and thus a higher level of perceived necessity for disease management including physical activity. We expect that chronically ill patients would visit health care professionals more frequently, thereby raising the probability of receiving physical activity advice or even a physical therapy prescription. Second, physical activity behaviour patterns for all seven types of physical activity seemed comparable among the four latent profile classes. The magnitude of the probability of executing each type of activity, however, differed among profile classes. The second profile class and thus the relatively healthy group, appeared to be associated with the highest levels of leisure time physical activity (e.g. walking, cycling, gardening, odd jobs and sports), in

spite of having the highest chance of liver disease or cirrhosis. This seems to confirm findings from previous research that showed that healthy persons had the highest physical activity [3]. Moreover, previous investigations had shown that skeletal muscle contraction alleviates symptoms of liver disease, lowers pain, reduces inflammation, improves oxygen delivery to the liver which enhances liver function and seems to delay severe muscle wasting which is common in advanced liver disease [28, 29]. Thus, directly noticeable benefits of physical activity might explain enhanced leisure time physical activity in patients with liver disease. However, it is important to recall that only 16 (0.5%) of our total population of 3,386 patients reported having liver disease and that a higher probability for leisure time activity levels may therefore be attributed more to this group's better health than to the elevated chance of liver disease. The probability of performing household chores was lowest in this latent profile class, whilst the probability of engaging in household activities was the highest compared to the other physical activity types in the other three profile classes. Overall, the probability of performing household chores was highest in the group with the least cardiovascular disease, cancer and rheumatoid arthritis. The probability of doing household activities might have been highest, because it is natural to want to stay at home as people grow older. Maintaining home care might make patients feel more independent, particularly those with the highest probability of having the most severe chronic diseases [30]. It is unclear why healthiest patients having the highest chance of liver disease or cirrhosis participated so infrequently in household activities.

The results of this study suggest that policymakers should promote increased physical activity levels among older individuals with a low probability for chronic. At the same time, health care providers should clearly emphasise the benefits of physical activity in patients with the highest probability of suffering from chronic diseases. Although, our sample was small, our results suggest that the reason why patients with liver disease or cirrhosis have the highest probability of engaging in leisure time physical activity and sports, in particular, could be because the benefits are directly noticeable in this group. If future research can confirm this hypothesis, it might be even more important to emphasise that patients with high probabilities for other chronic diseases could experience benefits from engaging in physical activity, though they may not be immediately noticeable.

Unanswered questions and future research

The present study was the first to integrate multimorbidity and physical activity in a latent profile analysis to establish a model of their relationship. Nevertheless, the design was cross-sectional and therefore future research is needed to reveal whether the multimorbidity - physical activity behaviour model suggests temporality and thus a causal relationship. In addition, to enhance interpretability and accuracy we propose the inclusion of other indicators associated with multimorbidity and/or physical activity, such as age, gender and living environment of participants.

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Chapter 9

General Discussion

MAIN FINDINGS

Regular physical activity is one of the most important things people can do for their health. Therefore, addressing factors that impede physical activity is of utmost importance. In this context the influence of multimorbidity appears to be relatively underrecognised and understudied despite the assumed significant burden on individuals and subsequent negative health consequences. The aim of the present thesis was to study the association between multimorbidity and physical activity. The first part of this thesis focuses on physical therapy outcome expressed in meters walking among patients with intermittent claudication and comorbidity who are referred to the physical therapist or directly access physical therapy for supervised exercise therapy. The second part of this thesis is an investigation of the association between multimorbidity and leisure-time physical activity in daily life measured as compliance with the Dutch physical activity guideline.

PART 1: PHYSICAL ACTIVITY AS OUTCOME IN MULTIMORBIDITY TREATMENT

To elucidate the challenges and the complexity of improving physical activity in people with multimorbidity, this dissertation started with a discussion about the difficulties of using single-disease guidelines to improve walking distance in patients with intermittent claudication and the comorbidities chronic obstructive pulmonary disease and knee osteoarthritis. It was highlighted that in the absence of physical therapy practice guidelines incorporating multimorbidity, experience-based evidence might in the short term help to guide physical therapists through the complex process of managing patients with comorbidity (chapter 2). After emphasising the challenges of current physical therapy practice, we identified current treatment of patients with intermittent claudication, chronic obstructive pulmonary disease and knee osteoarthritis in usual physical therapy care. Using a vignette design we investigated whether physical therapists make reasoned adaptations to evidence-based single-disease physiotherapy guideline recommendations when comorbidity influences the single-disease treatment. Our qualitative analysis showed that the majority of physical therapists make adaptations to evidence-based recommendations in case of comorbidity (chapter 3). We assumed that this is the case because comorbidity may influence physical therapy treatment outcomes. Therefore, we wanted to get more in-depth information about the influence patient characteristics and comorbidity might have on treatment progress and treatment outcome in usual physical therapy care. In usual physical therapy care patients with intermittent claudication are treated with supervised exercise therapy and treatment outcome is measured as improvement in initial claudication distance (maximum pain-free walking distance) and/or absolute claudication distance (maximum walking distance). Our results showed that females, patients at advanced age, patients with a high body-mass index and cardiovascular comorbidity are more likely to show less improvement in initial

claudication distance after physical therapy treatment (chapter 4). Since we found that some patient characteristics and comorbidity may reduce improvements in initial claudication distance after supervised exercise therapy, we hypothesised that expected treatment effects, as shown in research into supervised exercise therapy, fall short in physical therapists since the better and healthier patients are often included in randomised controlled trials. Hence, in chapter 5 we compared patient characteristics and treatment outcomes between randomised controlled trials that study the effect of supervised exercise therapy in patients with intermittent claudication and patients with intermittent claudication that were treated with supervised exercise therapy in usual physical therapy care. Note that to include as many good trials as possible the outcome maximum walking distance was used as comparator. The results showed that baseline characteristics of patients included in randomised controlled trials and patients treated in usual care were comparable. A statistically significant and clinically relevant difference in improvement in maximum walking distance between randomised controlled trials and usual care was found after three and six months of supervised exercise therapy, favouring patients treated in usual care.

PART 2: PHYSICAL ACTIVITY AND MULTIMORBIDITY IN DAILY LIFE

Once patients with comorbidity finalise physiotherapy treatment, it is important that adequate physical activity levels are maintained in daily life. Therefore, in the second part of this dissertation we identified chronic disease combinations that restrict physical activity behaviour so that health care professionals will be in a better position to help initiate and maintain adequate habitual physical activity levels in patients with multimorbidity (chapter 6 and 7). The lowest rate of physical activity was found in patients with cardiovascular disease, chronic respiratory disease and/or diabetes mellitus (chapter 6). The majority of patients with co-occurring diseases suffers from the presence of two chronic diseases simultaneously. Therefore, in a second step, we studied which chronic disease pairs lead to significantly constrained physical activity and whether having the combination of two diseases leads to even lower physical activity levels than what would be expected based on the effects of the diseases individually. The results showed that six chronic disease pairs led to more non-compliance with the Dutch physical activity guideline than expected based on the effects of the diseases individually. These chronic disease pairs were: chronic respiratory disease and severe back problems; migraine and inflammatory joint disease; chronic respiratory disease and severe kidney disease; chronic respiratory disease and inflammatory joint disease; inflammatory joint disease and rheumatoid arthritis; and rheumatoid arthritis and osteoarthritis of the knee, hips and hands (chapter 7). To do more justice to the complex and dynamic nature of multimorbidity and physical activity, we end this dissertation with a novelty in this research area. Our aim was to determine multimorbidity – physical activity profiles by using latent profile analysis including both chronic disease variables and physical

activity variables in the model. We identified four multimorbidity- physical activity behaviour profiles. The first latent profile class had the lowest prevalence of cardiovascular disease, cancer, rheumatoid arthritis and engaged the most in walking and performing household activities. The second profile class was the healthiest and had the highest prevalence of liver disease or cirrhosis, cycling, gardening, odd jobs and sports. The third group had the lowest prevalence of migraine, inflammatory joint disease and all types of physical activities except light household chores. The fourth group had the highest prevalence of all chronic diseases except for liver disease or cirrhosis and had moderate activity levels. Our results showed that multimorbidity does not seem to be the main obstacle to physical activity. Although, the pattern of physical activity behaviour for all seven types of activities seemed comparable among classes, there was a difference between the classes with respect to the magnitude to perform each type of activity.

INTERPRETATION OF STUDY FINDINGS

Coping with complexity: single-disease guidelines versus multiple-diseased patients

As defined by the Institute of Medicine, clinical guidelines are "statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options" [1]. Clinical guidelines can play an important role in improving physical therapy care and outcomes of physcial therapy care in patients with comorbidity, although perfect evidence based finetuning to all disease combinations will be unviable [2-4]. Currently, in the case of multimorbidity, existing physiotherapy guideline recommendations of the Royal Dutch Society for Physical Therapy (KNGF) require the physical therapist to read separate documents for each disease and to balance the benefits and risks of multiple recommended treatments. The KNGF guidelines for instance intermittent claudication [5], chronic obstructive pulmonary disease [6] and osteoarthritis [7] do not reflect the cumulative impact of treatment recommendations, synergies, cautions and outright contradictions which may result from combining all three recommendations. All three guidelines emphasise the importance of individual tailoring of exercise programmes in their generic introduction, albeit without further detailed discussion, despite evidence reported that 90% of patients with intermittent claudication, 83% of the patients with chronic obstructive pulmonary disease and 82% of the patients with osteoarthritis are multimorbid [8].

The majority of physical therapists (70%) reported to adapt treatment due to comorbidity, which implies that, the importance and necessity of comorbidity-related adaptations is certainly recognised by health professionals in physical therapy. However, guidance and consistency on how to adapt treatment seemed lacking, which was reflected in the huge variety of treatment adaptations that were reported. This heterogeneity suggests that physical therapists may struggle with uncertainty about whether and how to apply disease-specific guidelines to patients with intermittent claudication and comorbidity [9].

What the first part of this dissertation highlights is that the incorporation of non-index diseases into treatment recommendations seems to be necessary and inevitable for most physical therapists in order to optmize treatment.

If existing guidelines would appropriately cross-reference to other guidelines in case of synergistic or contradictory recommendations physical therapists could be alerted to take heed of comorbidity [10, 11]. Moreover, emphasising high risk interactions and impossibilities between recommendations may help to avoid harmful or unfeasible care and would enhance the appropriateness of existing guidelines to people with multimorbidity [12].

Regarding the applicability of physical therapy guidelines in case of comorbidity, we noticed a change for the better as the guideline on intermittent claudication was revised in 2015. The new guideline titled Symptomatic peripheral arterial disease [13] provides advice on the management of comorbidity as well as cross-references to other guidelines. It includes a detailed discussion about the influence of the most common comorbidities in patients with symptomatic peripheral arterial disease such as diabetes mellitus, chronic obstructive pulmonary disease, heart failure, angina pectoris, cerebrovascular accident and arthritis. However, none of these comorbidity-related recommendations included guidance for patients with more than one comorbidity. Doubtless, it will not be possible to generate good evidence for each combination of chronic diseases, but it seems important to have a conceptual understanding of how different disease interactions are likely to affect treatment and treatment outcomes.

In the context of supervised exercise therapy in patients with intermittent claudication, we found that age, sex, body-mass index and cardiovascular comorbidity are baseline variables that show differential degrees of an inverse association with improvements in initial claudication distance after supervised exercise therapy. Since, overall also a clear majority of previous small scale studies found less improvement in supervised exercise therapy treatment outcomes with regard to these variables, we feel confident that the presence of cardiovascular comorbidity in the diagnostic profile of patients with intermittent claudication has a significant inverse influence on physical therapy treatment outcome. A shortcoming is that we were not able to relate the response of the comorbid disorder to the content of supervised exercise therapy itself. To our knowledge, all previous research has also disregarded this issue. So an important question that remains is whether supervised exercise therapy treatment in patients with intermittent claudication also results in the amelioration of cardiovascular comorbid problems? Or, whether supervised exercise therapy in patients with intermittent claudication results in the deterioration of the associated cardiovascular comorbidity? The results of the present study contribute to our understanding of the combined effect of patient traits and comorbidity on the effectiveness of supervised exercise therapy in patients with intermittent claudication. Our results showed that the presence of comorbidity may impede the outcome of treatment for intermittent claudication. Therefore, this study once more endorses the need for comprehensive physical therapy guidelines to effectively care for patients with co-occurring cardiovascular diseases. The results of this study may add to the body of evidence underpinning new physical therapy guidelines.

Summarized, the results of the first part of this dissertation show that the simultaneous presentation of multiple diseases is a challenge for physical therapists that demands coordination and balanced judgement between disease-specific guideline recommendations of the Royal Dutch Society for Physical Therapy. A gap exists between the reality of physical therapy care of patients with comorbidity and physical therapy guideline recommendations that focus on isolated chronic conditions. Since, we found that comor-

bidity may influence actual treatment applied and treatment outcome, the quality of evidence and the strength of recommendations listed in existing guidelines should be evaluated for older adults with multimorbidity. New sections might be added to existing guidelines that address the altered effects of the most common comorbidities on the recommended treatment. Future research should therefore focus on identifying common comorbidities that potentially conflict with the existing disease specific KNGF treatment recommendations.

Scrutinising medical research and clinical practice: bridging two cultures

The aim of our study presented in chapter 5 was to assess the degree and impact of patient selection in randomised controlled trials by describing commonly used exclusion criteria and by comparing baseline characteristics and treatment responses of patients with intermittent claudication included in clinical trials and of patients with intermittent claudication treated in usual care. First, our results showed that baseline characteristics between randomised controlled trial participants and patients treated with supervised exercise therapy in usual care were comparable and did not suggest selection bias. On the one hand, we consider this a positive finding because it seems that the impaired generalisability of randomised controlled trial results, which originate from the eligibility criteria applied [14-16], do not hold true in physical therapy research studying the effects of supervised exercise therapy in patients with the index disease intermittent claudication. Nevertheless, we have to question the representativeness of the population of patients that follow supervised exercise therapy, in relation to all patients with intermittent claudication in the usual care setting. We hypothesize a selection to the better and healthier patients that follow supervised exercise therapy in usual physical therapy care. Supervised exercise therapy as first line treatment for intermittent claudication implies a lengthy exercise training program (at least six months [10]) combined with a change of lifestyle and increase of ambulatory activities [17]. Moreover, the first 20 treatment sessions of a supervised exercise therapy program have to be paid either directly by the patient or through additional insurance in the Netherlands. Both, the behaviour change component, the duration of supervised exercise therapy and the costs may cause a selection of the group of patients with intermittent claudication that follows supervised exercise therapy. Optimal would have been to compare patient characteristics of patients participating in randomized controlled trials and the ones treated in usual physiotherapy care with patient characteristics of all patients registered by the general practitioner with intermittent claudication. Regretfully, we were not able to do so due to restrictions in data access. Furthermore, we were only able to compare patients with intermittent claudication included in randomized controlled trials and patients with intermittent claudication treated in usual care on a limited set of registered characteristics. For this limited set of characteristics we state that randomized controlled trial participants and patients treated in usual care seem to be comparable. However, it might be

that there are other characteristics that differ between the two groups and may be responsible for the better outcomes in physical therapy care.

Second, we found greater improvements in maximum walking distance in patients with intermittent claudication that were treated in usual physical therapy care. Possible explanations for the underestimation of treatment effects in randomized controlled trials might be that the more resilient patients with intermittent claudication are more likely to consult their physical therapist for supervised exercise therapy; that the therapeutic qualities of therapists applying supervised exercise therapy are higher in usual care; and that additional home-based walking exercises that are part of usual care might have contributed to the larger improvements in walking distance after three and six months in usual physical therapy care.

From the results of our study we cautiously conclude that physical therapy randomized controlled trials investigating the effect of supervised exercise therapy in patients with intermittent claudication seem to provide an underestimation of treatment effects. Detailed methodological and contextual comparisons of supervised exercise therapy in physical therapy randomized controlled trials and supervised exercise therapy in usual care are needed to back up our findings.

Disease combinations associated with physical activity

In the average Dutch population of older adults, 68.6% comply with the Dutch physical activity guideline recommendation, which states that every older adult should accumulate up to 30 minutes or more of moderate intense physical activity (3 to 5 METs) on at least five, or preferably all days of the week [18]. Diminished physical activity levels have often been associated with the presence of chronic diseases [19, 20]. In chapters 6, 7 and 8 we studied how specific combinations of chronic diseases are associated with physical activity. The results of chapter 6 revealed the lowest rate of compliance with the Dutch physical activity guideline (55.8%) in patients with chronic respiratory disease, cardiovascular disease and/or diabetes mellitus. Overall a low variability in physical activity guideline compliance in patients with different chronic diseases has been found (compliance percentage fluctuated between 55.8% and 62.4% between the groups of patients with varying disease patterns). Thus, physical activity guideline compliance seems to be merely 5% to 10% less in older adults with chronic diseases and/or multimorbidity compared to older adults of the average Dutch population and even in the worst case still more than half of all patients do meet the recommended levels of physical activity, which illustrates that it is possible for many patients with chronic diseases to be physically active [21, 22]. However, sedentary behaviour should be considered in future studies as well, since it is expected that physical activity guidelines will be updated to include sedentary behaviour as well. Sedentary behaviour, has been defined as an energy expenditure ≤ 1.5 metabolic equivalents and a sitting or reclining posture [22]. Especially, of interest in the case of multimorbidity is that a positive association is assumed between sedentary behavior and chronic illness [20].

To illustrate the complex nature of multimorbidity and to see how active people are in different types of physical activity, we developed multimorbidity- physical activity behaviour profiles in Chapter 8. We did so because if there is interest in targeting physical activity interventions for patients with multimorbidity, the role of multimorbidity should be investigated in relation to a particular physical activity behaviour. We found four multimorbidity-physical activity behaviour profiles: The first latent profile class had the lowest prevalence of cardiovascular disease, cancer, rheumatoid arthritis and engaged the most in walking and performing household activities. The second profile class was the healthiest and had the highest prevalence of liver disease or cirrhosis, cycling, gardening, odd jobs and sports. The third group had the lowest prevalence of migraine, inflammatory joint disease and all types of physical activities except light household chores. The fourth group had the highest prevalence of all chronic diseases except for liver disease or cirrhosis and had moderate activity levels. Our results showed that physical activity behaviour patterns on all seven types of activity, i.e. walking, cycling, gardening, odd jobs, light and intense household activities and sports, were comparable among the four latent profile classes. Light household activities were done most. The likelihood of executing each type of activity however varied between the four profile classes. Despite the fact that the presence of specific chronic diseases hampers the likelihood of executing all seven physical activity types, the behaviour pattern across these seven activity types remained the same. It seems that all seven activity types, walking, cycling, gardening, light and intense household activities and sports are incorporated into people´s normal everyday life independently from the chronic disease pattern of the person.

Previous research demonstrated an inverse association between multimorbidity and physical activity [23-25]. However, all three studies used the sum of chronic diseases as measure for multimorbidity. For further exploration, we hypothesized that there might be certain chronic disease combinations that particularly worsen physical activity levels. The results of our investigations in chapters 6 and 8, however, suggest that there is a diverse influence of specific chronic disease combinations on physical activity, but that the disease combination itself does not make a salient contrast to physical activity levels and types of physical activity performed. To underpin our finding that the specific disease combination is not the main 'culprit' in the association between multimorbidity and physical activity, we went one step back and tested the association between the simple count of diseases and the seven physical activity types (Appendix 1, unpublished data). We found comparable overall physical activity levels between patients with no chronic disease, one, - two, - and three chronic diseases. Patients with four chronic diseases or five and more chronic conditions were significantly less physical active (Figure 1). Summarized, respective the total minutes spend on physical activity we found no difference in patients with three and less chronic diseases, however, a significant worsening in total minutes spend was found in patients with four and more chronic diseases.

Regarding the type of physical activity that is performed, we found in agreement with the results of our latent profile analysis, that regardless the number of chronic diseases most time is spent on light household activities, followed by walking and gardening activities. Moreover, time spent on cycling, sport and intense household activities becomes less as the number of chronic diseases a patient has increased. The association between the number of chronic diseases and physical activity was statistically significant. Decline in physical functioning is a normal process of aging and may be reflected in our finding that the first physical activities to give up on are for example sports and the ones that are maintained are basic activities supporting independent daily living.

The shape of the association between chronic diseases and physical activity

In chapter 7 we studied the shape of the association between two chronic diseases and physical inactivity. We were curious about whether the joint effect of two diseases is a combination of their independent effect of whether the joint effect of two diseases is greater than the combined independent effects (synergy) of two chronic diseases in the association between multimorbidity and physical inactivity. Remarkably, we found that in six chronic disease pairs the combination of two diseases leads to even more physical activity guideline non-compliance than expected based on the effects of the individual diseases. The fact that the association between chronic disease pairs and physical activity guideline compliance appears to be less than the individual effects of both individual diseases is in line with previous studies that highlight worse outcomes in those with multiple chronic diseases [20, 26]. However, to enhance understanding and clinical relevance, in depth investigations on the etiology, the course and the impact of chronic disease combinations on physical activity are needed [22, 27]. We propose using the inverse association between the six chronic disease pairs: (1) chronic respiratory disease and severe back problems; (2) migraine and inflammatory joint disease; (3) chronic respiratory disease and severe kidney disease; (4) chronic respiratory disease and inflammatory joint disease; (5) inflammatory joint disease and rheumatoid arthritis; (6) and rheumatoid arthritis and osteoarthritis of the knees, hips and hands as a starting point to assess the shape of the association between multimorbidity in physical inactivity in patients.

Multimorbidity complicates the challenge of policymakers and healthcare providers to determine the best approach to promote appropriate regular physical activity to the general public. More targeted efforts are needed to increase physical activity in those older adults that fail to meet recommended physical activity levels. If certain chronic diseases co-occur as presented in the previous section, health care providers should be alerted that these patients might display extra worse physical activity levels. Moreover, if patients report to have more than four chronic diseases again health care providers

should consider this as extra point of attention with respect to physical activity. In Chapter 6 we gave an idea of what chronic disease combinations (clusters) can be expected to co-occur in their association with physical activity. However, since these chronic disease combinations did not reoccur in our study on chronic disease pairs as we would have expected, more research is definitively needed to further explore the association between specific combinations of diseases and physical activity.

GENERAL METHODOLOGICAL REFLECTIONS

In the next paragraph, the challenges of the concept and measurement of multimorbidity and physical activity will be reviewed. Furthermore, the bi-directional association between multimorbidity and physical activity, the cross-sectional study design and issues of causality will be discussed. This paragraph will be finalized with implications for clinical practice and recommendations for future research.

The definition and measurement of multiple chronic diseases

Despite the growing number of people with multimorbidity, a universally accepted definition of multimorbidity is lacking [28]. First, consensus is required regarding the definition of a 'health condition'. In the literature various terminologies have been used interchangeably to describe health conditions of patients, including terms like 'diseases', 'ailments', 'conditions', 'disorders', 'illnesses' and 'health problems' [28-31]. Nevertheless, different terminologies might not be interpreted in the same way. It might for example be that some researchers/experts do not necessarily see a health problem as a disease. As a consequence varying definitions might include differing spectra of possible morbidities. In the present thesis we used the definition proposed by Boyd and Fortin [32]. According to this definition multimorbidity refers to any co-occurrence of two or more chronic conditions in the same individual, which may or may not interact with each other and where one condition is not necessarily more central or important than the other. Comorbidity refers to the presence of one or more additional disorders next to an index disease which has a central place [32]. We used the concept of comorbidity in the first part due to the explicit referral of our patients for supervised exercise therapy. Intermittent claudication was considered central and truly dominant in terms of treatment (outcome) determination. We used the definition of multimorbidity as proposed [32] because it goes beyond the spectrum of diseases, referring to conditions. The SMILE primary care data, which was used in the second part of this thesis, included for instance information about the presence of migraine, severe back problems and persistent injury from an accident, which might not that easily be denoted as a disease. To be able to include these conditions that fall outside the traditional disease model, the present definition fitted the aim of our investigation best.

Although, defining multimorbidity and comorbidity is the first problem that arises, there is increasing attention, as well as doubts, regarding the various methods of comorbidity assessment. To begin with, the number of diseases to be included in multimorbidity indices varies significantly between studies [33-35]. Existing instruments seem to include a range of between 4 to 102 diseases, with a majority of authors providing no reasons for their selection of diseases [35]. Moreover, some indices merely identify the presence of different conditions, while others apply different weights to each condition [34-36]. The way of obtaining data is also relevant for conclusions about the reliability and validity of the comorbidity and/or multimorbidity assessment. The completeness of data varies between data obtained from interviews, questionnaires, physical examination or prospectively and retrospectively recorded patient data. All these data sources have different purposes and hence concordance between different data sources in multimorbidity and comorbidity is known to be problematic [28]. Until now no gold-standard data source exists that provides the best comorbidity and/or multimorbidity estimates.

We conclude that the definition as well as the measurement instrument used, i.e. the type of data and the set of diseases on which the measurement of comorbidity and/or multimorbidity is based, is decisive for the estimation of the disease burden of a particular patient. The variety of approaches which are often related to the research aim, the study design and study population limit our understanding of multimorbidity because differences in the definition and its measurement make it hard to compare results from different studies.

Challenges of the concept and measurement of physical activity

Accurately measuring physical activity is a prerequisite to determine the association between multimorbidity and physical activity. In Chapters 6 and 7 physical activity was measured as compliance with the Dutch physical activity guideline, which states that every adult should accumulate 30 minutes or more of moderate intense physical activity (3 to 5 METs) on at least five, or preferably all days of the week [18]. Although moderate intense physical activity levels can be defined and expressed in the Metabolic Equivalents of Tasks (MET) [37] it should be acknowledged that physical fitness and physical capacity of patients with multimorbidity varies tremendously. For some, slow walking is not intense, while for others this is already perceived as a moderately intense performance. Furthermore, the Dutch physical activity recommendation does not balance issues regarding feasibility in those with chronic diseases. We think that the Dutch physical activity guideline recommendation can be applied to older adults with chronic disease and/or multimorbidity, however, due to the variation of functional limitations and decrease in physical capacity and fitness that accompany with the presence of chronic diseases the recommendation might need to be adjusted based on exercise capacity, specific health risks and limitations of a person.

In Chapter 8 we measured physical activity across different domains: walking, cycling, gardening, odd jobs, household activities and sport as they are assessed in the Short Questionnaire to Assess Physical Activity (SQUASH). The SQUASH questionnaire is a commonly used, reliable and valid tool to assess physical activity at population level and has also been applied in the SMILE cohort study to measure physical activity in all participants [18]. Although, the SQUASH questionnaire has proven to be appropriate, easy to administer, inexpensive and applicable on a large scale [18], the validity of self-reported subjective physical activity measures in general is still disputed [38]. It is well known, that individuals are reasonably, but not highly accurate in self-reports of physical activity [39]. Most people tend to underestimate their participation in sedentary activity and to overestimate their involvement in physical activity [38-40]. In future studies, improvements in physical activity measurement could be facilitated by electronic monitoring, which often seems to be a highly reliable and valid objective measurement alternative for assessing physical activity behaviour on population level [41, 42]. However, until now most electronic gadgets used to objectively measure physical activity are not accurate in the measurement of activities or do not involve footfalls such as cycling, swimming and upper body movement (i.e. household activities, weight lifting). We await the developments and hope that in the future electronic movement monitors are able to provide more accurate information regarding habitual physical activity since lifestyle physical activity is often highly habitual and requires merely minimal conscious processing [40], which additionally makes self-reported data questionable.

Cross-sectional design and causation

Chapters 6 to 8 of the present thesis contain articles that are cross-sectionally designed and it is therefore important to review whether the association between multimorbidity and physical activity might suggest temporality and thus a causal relationship [43, 44]. In the chapters themselves, results have been interpreted with caution, because exposure and outcome have been measured at the same time and therefore it was not possible to distinguish cause from effect. Overall, the association between multimorbidity and physical activity seems to be bi-directional (Figure 1A). On the one hand, physical inactivity seems to contribute to the development of chronic diseases and/or multimorbidity, while on the other being diseased constitutes a risk of ending in a downward spiral of physical inactivity and sedentary behaviour (Figure 1B), since being diseased is often a cause for a lack of regular physical activity [45]. This vicious circle of deconditioning and related physical inactivity increases the vulnerability of patients to further health problems and chronic diseases [46, 47].

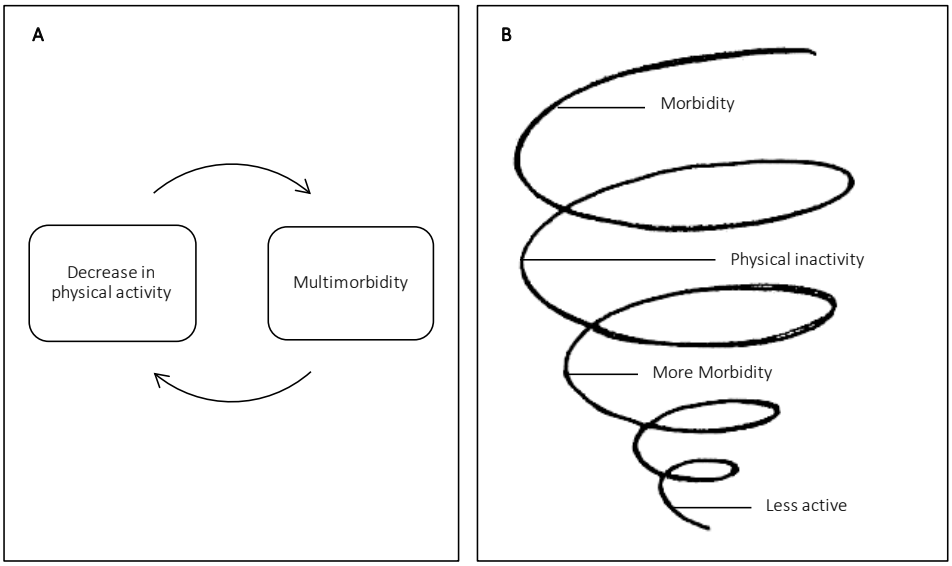

Figure 1. Vicious cycle and downward spiral of multimorbidity and physical inactivity.

Given the inconclusiveness of the association between multimorbidity and physical activity we consider regular physical activity dual by means of primary disease prevention and secondary disease treatment. The advantage of physical activity is that unlike medication, physical activity changes the underlying physiological mechanisms and is almost free of side-effects. Moreover, physiological changes brought on by regular physical activity are not beneficial for one disease, but all body systems are altered and improved simultaneously. This is why physical activity is also often described as a polypill to prevent or treat almost every chronic disease [48, 49]. To illustrate, physical activity improves the uptake of glucose from the blood and thereby reduces the stress on the pancreas (diabetes mellitus); causes a greater stroke volume and cardiac output, lowers heart rate and mean arterial pressure at rest (cardiovascular disease and hypertension); enhances bone mineral density (osteoporosis); decreases dynamic hyperinflation and dyspnea and leads to fewer exacerbations (chronic respiratory disease); and alters several inflammatory factors, improves immune response and specifically antioxidant defence mechanisms (cancer)(Figure 2) [50].

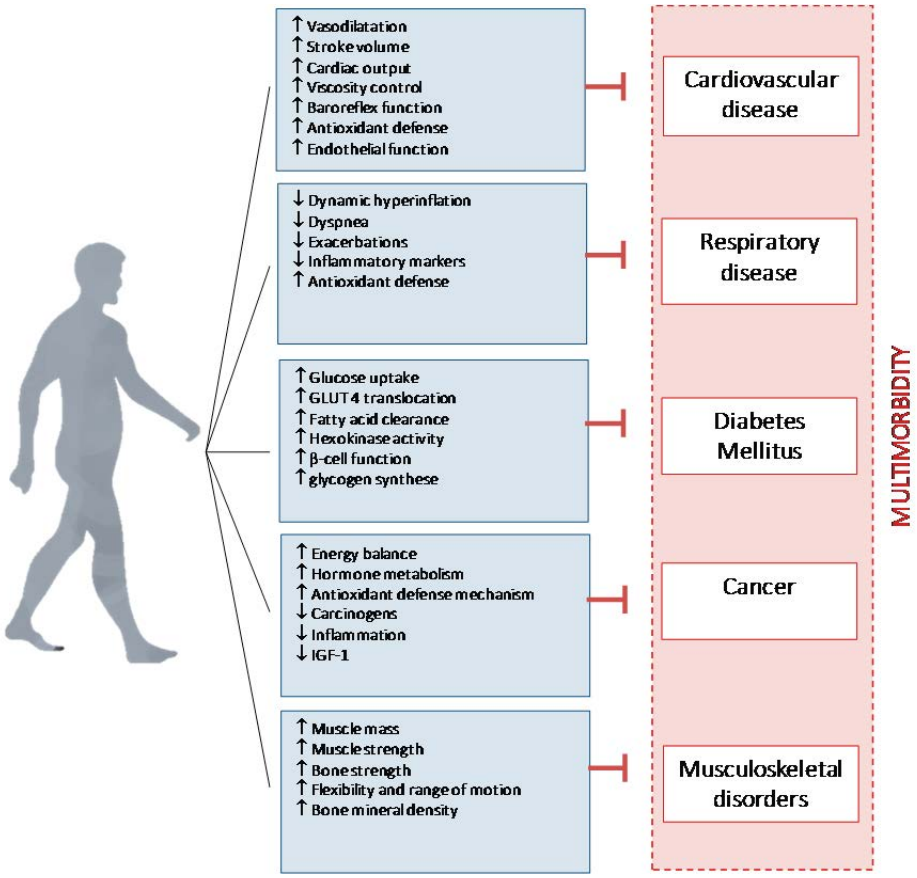

Figure 2. Physiological changes brought on by regular physical activity are not only beneficial for a single disease.

Given that physical activity is beneficial for most (chronic) diseases, physical activity should be incorporated in all prevention and treatment strategies to improve quality of life, reduce chronic disease related deaths and healthcare costs. Future research on longitudinally collected data is necessary to provide information on the temporality of the association between multimorbidity and physical inactivity. Moreover, prospectively designed research studies should add information on whether changes in physical activity levels are related to concurrent changes in (severity) and the (perceived) burden of chronic diseases.

Since, the association between multimorbidity and physical activity is bi-directionally our results could be interpreted in two ways. On the one hand, it might be that insufficient physical activity levels have caused the specific combinations of chronic diseases we found in our patient population; on the other it might be that the presence of spe-

cific combinations of chronic diseases causes patients to become less physically active. To our opinion the second seems more likely [51]. Several risk factors are involved in the development of chronic diseases and it might be that a specific combination of risk factors, together with genetic trait variations, other external and environmental factors lead to different chronic disease combinations in patients. However, that would imply a certain level of independence between the different chronic diseases, which seems not likely, since most chronic diseases share common risk factors [52]. Therefore, from our point of view it seems more likely that a specific combination of chronic diseases might hamper physical activity in patients. In fact in chapter four we found that not all comorbidities significantly worsen physical therapy treatment outcome and that it does matter what kind of comorbidity a patient has. Still, the results of the present thesis should be interpreted with caution since they do not allow us to present a causal connection.

IMPLICATIONS FOR CLINICAL PRACTICE AND RECOMMENDATIONS FOR FUTURE RESEARCH

This dissertation contains a first, thorough and novel analysis of the association between multimorbidity and physical activity. This is of importance, since research of the association between multimorbidity and health, - or behavioural outcomes is lacking, but urgently needed. Furthermore, this thesis is particularly interesting as it not just links multimorbidity to physical activity, but studies a diverse range of physical activity outcome measures (i.e. physical activity expressed in meters walked; measured as compliance with the national physical activity norm; and specific physical activity behaviour performed).

Current guidelines fail to address how to optimally integrate existing single-disease guidelines in patients with multiple co-occurring diseases. They are framed as recommendations to act, however guidelines that target treatment for patients with comorbidity should focus more on a comparative illustration of the benefits and harms of different recommendations including explicit cross-referencing. The revised KNGF guideline on symptomatic peripheral arterial disease [10] makes a first step in the right direction by incorporating recommendations for frequently co-occurring comorbidities. We would suggest to additionally make physical therapists aware of the influence of more than four chronic diseases on overall physical activity. Since, a main limitation of chapter 3 was that the effect of treatment adaptations on treatment outcome remains unknown and conversely in chapter 4 the black box of applied treatment existed, it is necessary to connect this information to get a complete picture of successful treatment elements. We propose a prospective longitudinal standard physiotherapy care cohort study in which highly trained physical therapists carefully record treatment adaptations, underlying rationales for adaptation and treatment outcomes over time.

Furthermore, we highlighted that baseline characteristics of patients with intermittent claudication included in randomised controlled trials and patients with intermittent claudication treated in usual care were comparable. This suggests that randomised controlled trial eligibility criteria are implicitly used by professionals referring patients. It might be worthwhile to find out what the characteristic of the whole population of patients with intermittent claudication are, regardless whether they receive physical therapy or not. In relation to this, research on the reasons for no supervised exercise therapy participation of patients with intermittent claudication in usual care might enhance our understanding regarding a possibly selected group of patients that receives supervised exercise therapy as part of usual physical therapy care.

In addition, contrary to our expectations we found that improvement in supervised exercise therapy treatment response was greater in usual care compared to randomised controlled trials. In depth information on possible supervised exercise therapy

adaptations and treatment annexations in usual physical therapy care would provide useful information to enhance the portability of treatment effects between research and standard physiotherapy care. Meanwhile, a nationwide community based supervised exercise therapy network has been founded. Via this network physical therapists have been trained to provide high quality supervised exercise therapy in patients with the index disease intermittent claudication. This progress in expertise of care providers resulting in higher quality of supervised exercise therapy care might result in even a larger discrepancy between physical therapy treatment effectiveness presented in randomized controlled trials and usual care because their expertise has become even better and they have the flexibility to adjust their treatment to the patient; in a trial this would be considered a protocol violation. Therefore, it might be interesting to compare supervised exercise therapy effectiveness presented in randomized controlled trials with more recent data from usual physical therapy.

Finally, this thesis illustrates that it is worthwhile to look at the association between specific combinations of chronic diseases and physical activity, but that chronic diseases might not be the main determinant for physical inactivity. We suggest to extent the current exploratory model explaining physical activity behaviour, to include social cognitive concepts as motivation and self-efficacy, since these seem to be more strongly associated with physical activity behaviour [96]. Since, physical activity has been described as 'polypill' playing a crucial role in the prevention and treatment of almost every chronic disease [97, 98], the main challenge is to support patients in a way that they engage in physical activity in the long-term [99, 100]. However, it seems that the importance of helping, advising and encouraging patients to become physically active or to maintain physical activity levels is not always recognised in routine clinical practice. To illustrate, previous research reported that 39% of patients with heart failure did not receive any physical activity advice from their cardiologist [101] and no physical activity advice from the cardiologist was received by 37% of patients with congenital heart diseases [102]. It is important that healthcare providers feel more responsibility to support and advise their patients regarding their physical activity behaviour. With support we not just mean physical activity advice, but also referral for physical therapy. We presented chronic disease combination that extra hinder physical activity and therefore provide some guidance on which patients might be most in need for advice and/or referral.

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Appendix

APPENDIX (UNPUBLISHED DATA)

APPENDIX 1. THE NUMBER OF CHRONIC DISEASES AND PHYSICAL ACTIVITY

Association between the number of chronic diseases and physical activity

We studied the association between the number of chronic diseases and physical activity behaviour. Since, the N of patients with five chronic diseases (n=30), six chronic diseases (n=9) and seven chronic diseases (n=6) was low, these three categories were combined into 'five and more chronic diseases (n=45)'. Descriptive statistics were used to examine the mean time spend on each type of physical activity given the number of chronic diseases (none, one, two, three, four and five and more) present (Table 1). Linear regression analysis was performed to study whether the association between the number of chronic diseases and physical activity (total amount of minutes being active per day) was statistically significant.

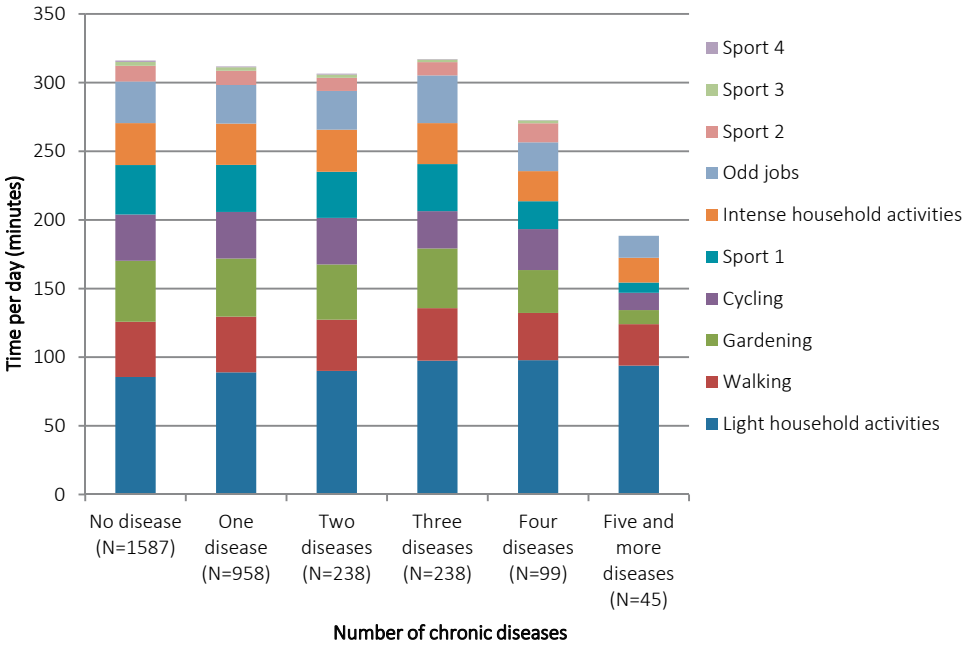

Figure 1. The association between the number of chronic disease and physical activity behaviour.

Summary

This thesis considers the association between multimorbidity and physical activity with the aim to give directions for targeting patient treatment.

Chapter 1 defines the concepts multimorbidity and comorbidity that are used in this dissertation and provides background information on the index disease peripheral arterial disease that is the central theme in the first part of this dissertation. Peripheral arterial disease is a circulatory problem in which narrowed arteries reduce blood flow to the limbs. This causes symptoms as pain and/or tiredness in the leg(s) during walking, commonly referred to as intermittent claudication. As a result walking distance is impaired. The primary treatment modality for patients with intermittent claudication is treadmill walking to near maximum pain levels supervised by a physical therapist or any other exercise specialist. Supervised exercise therapy has proven to lead to significant improvements of maximum walking distance in patients with intermittent claudication. Mechanisms responsible for improvements in walking distance and underlying peripheral physiological adaptations that occur due to supervised exercise therapy are improved endothelial function, improved mitochondrial energetics, increased collateral flow and decreased inflammatory levels. Both supervised exercise therapy treatment and subsequent success may be negatively influenced by comorbidity and/or multimorbidity. This applies to daily physical activity as well. Considering the growing amount of patients with multimorbidity and the fact that physical activity is seen as number one lifestyle intervention for patients with chronic diseases, a better understanding of the association between multimorbidity and physical activity will support disease prevention and disease treatment by facilitating the development of more targeted counseling strategies among this clientele.

PART 1: PHYSICAL ACTIVITY AS OUTCOME IN MULTIMORBIDITY TREATMENT

The first part of this dissertation concentrates on physical activity and multimorbidity treatment. Patients with intermittent claudication (index disease) and comorbidity who are referred to the physical therapist or direct access physical therapy care are the focus.

To elucidate the complexity of using single-disease guidelines to improve walking distances in patients with intermittent claudication, implications of the co-occurrence of two common comorbidities, chronic obstructive pulmonary disease and knee osteoarthritis, were illustrated. Chapter 2 started with a discussion paper in which the multiplicity of treatment options that arise when a patient suffers from comorbidity were exemplified. The challenge for physical therapists is to weight the impact of comorbidities in relation to physical therapy (evidence-based) treatment options and outcomes. This challenge must be acknowledged, along with the maybe unfeasible process of gathering

scientific evidence from (randomised controlled) trials about how to treat patients with diverse comorbidities in physical therapy care. This requires us to look for other more short-term or viable solutions to provide guidance for those in need. We suggest that providing meaningful consented experience-based evidence on the benefits and harms of treatment recommendations for individual patients might provide a short-term solution that may systematically support physical therapists in making treatment decisions for patients with comorbidity.

After our recapitalization of the challenges of comorbidity in current physical therapy practice we tried to shed light on the current treatment of patients with intermittent claudication and comorbidities in usual physiotherapy care. Therefore, in chapter 3 we assessed qualitatively whether physiotherapists make reasoned adaptations to evidence based treatment recommendations when comorbidities influence the single disease treatment. We examined the impact of the comorbidities chronic obstructive pulmonary disease and knee osteoarthritis on a physical therapy treatment recommendation in a hypothetical 69 year old woman with the index disease intermittent claudication using a vignette design. The results showed that thirty percent of the physical therapists do not adjust treatment despite comorbidity. Another 30% partly adapted the treatment plan when comorbidity was added and the presence of comorbidity encouraged 40% to abandon guideline recommendations and to create an individualized treatment plan based on the perceived health needs of the vignette patient. We concluded that the majority of physical therapists make adaptations to evidence-based recommendations when comorbidity is present. We hypothesize they do so, because comorbidity was expected to influence treatment progress and treatment outcome unfavorably.

To investigate the influence of comorbidity on treatment outcome quantitatively, we studied in chapter 4 whether patient characteristics and comorbidity influence maximum walking distance after 1, 3, 6 and 12 months of supervised exercise therapy in 2295 patients with intermittent claudication. We executed a retrospective secondary analysis on prospectively collected electronic medical record data. All patients were treated with supervised exercise therapy according to the guideline intermittent claudication of the Royal Dutch Society for Physiotherapy. For this research field an innovative element of this analysis is the acknowledgement of the hierarchical data structure by applying three-level mixed linear regression analysis to study the association of patient characteristics and comorbidity on maximum pain-free walking distance measured at 1, 3, 6 and 12 months after baseline. Being female, advanced age, having a high body-mass index and cardiac comorbidity were associated with less improvement in maximum-pain free walking distance at all time points. We concluded that specific patient characteristics worsen physical therapy treatment outcomes.

Since we found that patient characteristics and comorbidity reduce improvements in walking distance after supervised exercise therapy, we hypothesized that expected treatment effects shown in research of supervised exercise therapy fall short in physical therapists since the better and healthier patients are often included in randomized controlled trials. Hence, in chapter 5 we present the first study that assesses the degree and impact of patient selection in randomized controlled trials by comparing patient characteristics and treatment outcomes of randomized controlled trials on supervised exercise therapy in patients with intermittent claudication with patients with intermittent claudication that received supervised exercise therapy in the context of usual physiotherapy care at baseline and after three and six months. The results refuted our a-priori hypothesis. We found that baseline characteristics between randomized controlled trial participants and patients treated in usual care were comparable and did not suggest (structural) selection bias. Interestingly, when we studied differences in treatment response seen in randomized controlled trials and usual care, we found significant and clinically relevant differences in treatment response at three and six months favoring patients treated in usual care. This difference suggests an underestimation of the treatment benefits described in randomized controlled trials that are unlikely explained by differences in patient selection and intervention applied.

PART 2: PHYSICAL ACTIVITY AND MULTIMORBIDITY IN DAILY LIFE

The second part of this dissertation focuses on the relationship of daily leisure-time physical activity and multimorbidity. Once patients with comorbidity finalize physical therapy treatment, it is important that adequate physical activity levels are maintained in daily life. Given the growing number of patients with multimorbidity, we questioned whether it is possible to determine who will present initiation or maintenance problems concerning achieving optimal day-to-day physical activity levels.

Chapter 6 presents the first study in the field of multimorbidity research that links clusters of multiple chronic diseases with compliance with the Dutch physical activity guideline, which states that every adult should accumulate 30 minutes or more of moderate intense physical activity (3 to 5 MET) on at least five, preferably all days of the week. Ward's agglomerative hierarchical clustering and K-means clustering was executed on cross-sectional data of 3,386 patients from the Dutch cohort *S*tudy of *M*edical *I*nformation and *L*ifestyle in *E*indhoven (SMILE). Patients with liver disease, severe back problems, rheumatoid arthritis, osteoarthritis of the knees, hips and hands and inflammatory joint disease showed the highest rate of physical activity guideline compliance. The lowest rate of physical activity guideline compliance was reported in patients with cardiovascular disease, chronic respiratory disease and diabetes mellitus. We concluded that family physicians and physiotherapists should help and facilitate especially patients

with cardiovascular disease, chronic respiratory disease and diabetes mellitus to initiate and maintain adequate physical activity levels.

Because the majority of patients with co-occurring diseases suffer from the presence of two chronic diseases simultaneously, we were curious about which chronic disease pairs are associated with inadequate physical activity levels. While doing so we decided to add a second completely new layer to the field of multimorbidity research and to our investigation and additionally assessed whether having the combination of two diseases leads to even worse physical activity levels than would be expected based on the effect of the diseases individually. Therefore, in chapter 7 we studied the extent and the shape of the association between chronic disease pairs and compliance with the Dutch physical activity guideline. Chi-square statistics were used to test whether there was an inverse association between 105 chronic disease pairs and compliance with the Dutch physical activity guideline. To study the separate and joint effects of chronic diseases on compliance with the Dutch physical activity guideline a logistic regression analysis was executed. The results showed that the chronic disease pairs: chronic respiratory disease and severe back problems; migraine and inflammatory joint disease; chronic respiratory disease and severe kidney disease; chronic respiratory disease and inflammatory joint disease; inflammatory joint disease and rheumatoid arthritis; and rheumatoid arthritis and osteoarthritis of the knee, hips and hands lead to even more non-compliance with the Dutch PA guideline than what would be expected on the effects of the diseases individually. Our results may alert health care professionals towards the possibility of extra low physical activity levels in patients with one of these six chronic disease pairs.

Since it seemed that the combination of chronic diseases is the landmark in the association between multimorbidity and physical activity, we decided to finalize this dissertation with a novelty in the research area of multimorbidity and physical activity. The aim of chapter 8 was to compile a multimorbidity- physical activity behavior profile. We used latent profile analysis and included measurements of fifteen chronic diseases and seven different physical activity types at once into our model. We identified four latent profile classes. The first group had the lowest prevalence of cardiovascular disease, cancer and rheumatoid arthritis and was very active in walking and household activities. The second group was the relatively healthiest with the highest prevalence of liver disease and engaged most in cycling, gardening, odd jobs and sports. The third group had the lowest prevalence of migraine, inflammatory joint disease and all physical activity types except for light household activities. The fourth group had the highest prevalence on all chronic diseases except for liver disease and showed moderate activity levels on all seven physical activity types. From our results we conclude that chronic diseases seem not to be the main obstacle to physical activity, since the highest probability of most chronic diseases was linked with moderate physical levels. Furthermore, among all four latent profile classes physical activity behavior patterns seemed comparable with the highest

probability to perform household chores, which might be natural since older adults want to stay at home and maintain independence even in case of the highest probabilities for the most severe chronic diseases.

Chapter 9 discusses our results, presents methodological reflections and provides recommendations for clinical practice and future research. The results of the first part of our dissertation picture how current Dutch physical therapy guidelines may fail to address how to optimally integrate single-disease recommendations in patients with multimorbidity. Since the main limitation of chapter 3 was that the effect of guideline recommendation adaptations on treatment outcome remained unknown and the other way around in chapter 4 the treatment preceding the comorbidity-influenced treatment outcome assessment was unspecified, future research should connect this information in order to provide a complete picture. We propose a prospective longitudinal standard physiotherapy cohort study in which physical therapists precisely note treatment adaptations, rationales for treatment adaptations made and treatment outcomes over time.

Moreover, we found that baseline characteristics of patients with intermittent claudication included in randomised controlled trials and patients with intermittent claudication treated in usual care were comparable, however that improvement in supervised exercise therapy treatment response was greater in usual physical therapy care. Since, in 2011 a nationwide community based supervised exercise therapy network (ClaudicatioNet) has been founded with the aim to train physical therapists to provide high quality supervised exercise therapy. It might be interesting to compare supervised exercise therapy effectiveness presented in randomized controlled trials with more recent data from usual physical therapy. A potential improvement in quality of supervised exercise therapy might result in even a larger discrepancy between physical therapy effectiveness presented in RCTs and usual care.

In the last part of this dissertation clusters and profiles of patients were brought up that in different ways were linked with physical activity levels and types of activities. Our results illustrated that it is worthwhile to look at the association between specific chronic disease combinations and physical activity, but that chronic diseases might not be the main obstacle to be physically active. Since, the design of the studies presented in chapter 6 to 8 was cross-sectional, future longitudinal research is needed to reveal whether the multimorbidity- physical activity behaviour profile model suggests temporality and thus a causal relationship. To enhance fidelity we propose to also include other variables associated with multimorbidity and physical activity such as age, sex, living environment and psychosocial factors into the analysis and to extend the analysis towards structural equation models.

Zusammenfassung

Die vorliegende Arbeit beschäftigt sich mit der Wechselwirkung von Multimorbidität und Bewegung.

Kapitel 1 definiert Multimorbidität (das gleichzeitige Bestehen mehrerer Erkrankungen bei einem Patienten) und Komorbidität (das Auftreten zusätzlicher Erkrankungen im Rahmen einer definierten Indexerkrankung). Weiterhin wird in diesem Kapitel die Periphere Arterielle Verschlusskrankheit (auch Schaufensterkrankheit genannt) erklärt, da diese Erkrankung den ersten Teil dieser Dissertation prägt. Die Periphere Arterielle Verschlusskrankheit ist die häufigste Erscheinungsform der Arteriosklerose in der verengte Arterien die Durchblutung in den Extremitäten verringern. Dies kann zu Schmerzen und Müdigkeit in den Beinen beim Gehen führen. Patienten können oft nur kurze Entfernungen ohne Schmerzen gehen und vermeiden daher längere Gehstrecken. In Folge dessen, verringert sich die Schmerztoleranz und der Radius in dem sich der Patient schmerzfrei bewegen kann und wird der Patient dadurch im Alltag eingeschränkt. Zudem haben Patienten häufig eine hohe Koinzidenz koronarer Herzerkrankungen und Durchblutungsstörungen. Dieses Konglomerat an Symptomen und Erkrankungen limitiert die Lebenserwartung von Patienten mit Claudicatio Intermittens.

Die primäre Behandlungsmethode für Patienten mit Claudicatio Intermittens ist, neben der Behandlung der vaskulären Risikofaktoren, strukturiertes Gehtraining auf einem Laufband unter Betreuung eines Physiotherapeuten. Viele evidenzbasierte Studien belegen, dass betreutes Gehtraining zu erheblichen Verbesserungen der maximalen Gehstrecke bei Patienten mit Claudicatio Intermittens führt. Mechanismen, die zur Verbesserungen der maximalen Gehstrecke führen sind unter anderem: Optimierung der kollateralen Blutverteilung, verbesserte Kapillarisierung der peripheren Muskeln, eine reformierte Endothelfunktion, verbesserte mitochondriale Energetik, erhöhte Durchblutung und verringerte Entzündungswerte. Sowohl das strukturierte Gehtraining also auch die damit verbundenen Behandlungserfolge werden negativ durch Komorbidität und / oder Multimorbidität beeinflusst. Ein besseres Verständnis des Zusammenhangs zwischen Claudicatio Intermittens, Komorbidität und Bewegung kann einen spezifischeren Behandlungsplan ermöglichen.

TEIL 1: BEWEGUNG ALS TEIL DER BEHANDLUNG VON CLAUDICATIO INTERMITTENS UND KOMORBIDITÄT

Der erste Teil der Dissertation konzentriert sich auf Bewegung als Teil der physiotherapeutischen Behandlung von Patienten mit Claudicatio Intermittens und Komorbidität. Die heutigen evidenzbasierten Leitlinien, die als Handlungs- und Entscheidungskorridore für Patienten und Leistungserbringer eingesetzt werden, berücksichtigen keine Patienten mit Komorbidität. Anhand des Kasus einer multimorbiden Patientin wird die Komplexität von Krankheits-spezifischen, klinischen Leitlinien und die Komplexität der Be-

handlung von Patienten mit Claudicatio Intermittens und bestehender Komorbidität verdeutlicht. Die hypothetische Patientin aus dem Kasus ist weiblich, 69 Jahre alt und leidet an Claudicatio Intermittens und den Komorbiditäten chronisch obstruktive Atemwegserkrankung (COPD) und Kniearthrose. Kapitel 2 beginnt mit einer wissenschaftlichen Diskussion über die Vielzahl von vorgestellten Behandlungsmöglichkeiten für multimorbide Patienten. Die Herausforderung für Physiotherapeuten besteht darin einen fallspezifischen Behandlungsplan zu entwerfen. Ein Mangel an wissenschaftlichen Erkenntnissen aus randomisierten kontrollierten Studien über die Behandlung von Patienten mit Claudicatio Intermittens und Komorbidität erschwert das Erstellen eines Behandlungsplans. Jedoch ist die Ausarbeitung von wissenschaftlicher Evidenz für alle möglichen und häufigen Krankheitskombinationen bei Claudicatio Intermittens unmöglich, da aufgrund der Vielzahl an Kombinationen eine unerreichbar große Studienpopulation notwendig wäre. Erfahrungsbasierte Evidenz, könnte ein Weg sein, die gegenwärtige Praxis wissenschaftlich zu untermauern. Der Kerngedanke besteht darin, mit Hilfe von elektronischen Patientendaten implizite Verbindungen zwischen neuen Patienten und Patienten, die in der Vergangenheit behandelt wurden, herzustellen. Zusammenhänge zwischen der angewendeten physiotherapeutischen Behandlung und dem erzielten Behandlungserfolg, eines in der Vergangenheit behandelten Patienten mit vergleichbaren Eigenschaften und Krankheitskombinationen des noch zu behandelnden "neuen" Patienten könnten dann, als Leitfaden fungieren. Bereits existierendes Wissen neu und systematisch zu nutzen könnte ein Ansatz sein, um Physiotherapeuten im komplexen Management von multimorbiden Patienten zu unterstützen.

Nach unserer Rekapitulation der Herausforderungen die Komorbidität bei Patienten mit Claudicatio Intermittens mit sich mitbringt, haben wir die derzeitige physiotherapeutische Behandlung von Patienten mit Claudicatio Intermittens und Komorbidität untersucht. In Kapitel 3 untersuchten wir anhand eines fiktiven Patientencasus, ob Physiotherapeuten begründet von der krankheitsspezifischen, klinischen Leitlinie für Claudicatio Intermittens abweichen, wenn Komorbidität chronisch obstruktive Atemwegserkrankung (COPD) oder Kniearthrose die Behandlung beeinflusst. Die Ergebnisse unserer Studie zeigten dass 30% der Physiotherapeuten trotz der Komorbiditäten chronisch obstruktive Atemwegserkrankung (COPD) und Kniearthrose der krankheitsspezifischen Behandlungsempfehlung für Claudicatio Intermittens folgten. Weitere 30% veränderten teilweise die Behandlungsempfehlung aufgrund der anwesenden Komorbiditäten. Beide Komorbiditäten führten dazu, dass 40% der Physiotherapeuten die Leitlinienempfehlungen aller drei Krankheitsbilder losgelassen haben und einen individuellen Behandlungsplan erstellt haben. Aus unseren Ergebnissen konnten wir schlussfolgern, dass die Mehrheit der Physiotherapeuten (70%) von krankheitsspezifischen Leitlinienempfehlungen abweicht, wenn Komorbidität eine Rolle spielt. Wir vermuteten das dies der Fall ist weil Komorbidität sowohl den Behandelfortschritt, als auch das Behandlungsergebnis negativ beeinflusst.

Um den Einfluss von Komorbidität auf das Behandlungsergebnis quantitativ zu erforschen untersuchten wir bei 2295 Claudicatio Intermittens Patienten (Kapitel 4) ob bestimmte Patienteneigenschaften und Komorbiditäten die Verbesserung der maximale Gehstrecke nach ein, drei, sechs und 12 Monaten strukturiertem Gehtraining beeinflussen. Wir führten eine retrospektive Sekundäranalyse von prospektiv gesammelten Daten aus Patientenakten aus. Alle Patienten wurden nach den Behandlungsempfehlungen der Leitlinie Claudicatio Intermittens der Königlichen Niederländischen Gesellschaft für Physiotherapie behandelt. In einer Drei-Ebenen Regressionsanalyse haben wir berücksichtigt das Patienten von unterschiedlichen Therapeuten behandelt wurden. Unsere Ergebnisse zeigten, dass ein weibliches Geschlecht, ein fortgeschrittenes Alter, ein hoher Body-Mass-Index und kardiovaskuläre Komorbiditäten mit geringeren Verbesserungen der maximalen Gehstrecke zusammenhängen. Daraus konkludierten wir, dass bestimmte Patientenmerkmale und Komorbiditäten physiotherapeutische Behandlungsergebnisse verschlechtern.

Da bestimmte Patientenmerkmale und Komorbiditäten den physiotherapeutischen Behandlungserfolg zu beeinflussen scheinen haben wir die Hypothese aufgestellt, dass der Behandlungserfolg aus randomisierten kontrollierten wissenschaftlichen Studien, den Behandlungserfolg in der täglichen Praxis überschätzt, da Studienteilnehmer oftmals „gesünder“ sind als Patienten. In Kapitel 5 präsentieren wir die erste Studie welche die Auswirkungen der Auswahl von Patienten in randomisierten kontrollieren Studien beurteilt. Patientenmerkmale und Behandlungserfolge von Studienteilnehmern und Patienten die dieselbe Therapie im Rahmen der üblichen Rehabilitationspflege erhalten haben wurden zu Beginn der Studie und nach drei und sechs Monaten überwacht und verglichen. Die Ergebnisse widerlegten unsere Hypothese, dass sich Patientenmerkmale und Komorbiditäten von Patienten in wissenschaftlichen Studien von Patienten aus der täglichen physiotherapeutischen Praxis unterscheiden. Dies deutet nicht auf einen strukturellen Selektionseffekt bei der Auswahl der Teilnehmer von randomisierten kontrollieren Studien. Interessanterweise, fanden wir statistisch signifikante und klinisch relevante Unterschiede in den Behandlungserfolgen nach drei und sechs Monaten Gehtraining. Behandelerfolge waren entgegengesetzt unserer Erwartungen geringer in den randomisierten kontrollieren Studien. Dies suggeriert eine Unterschätzung der Effektivität des Gehtrainings. Diese Unterbewertung konnte weder durch die Auswahl von teilnehmenden Patienten noch durch Unterschiede des angewandten Gehtrainingsprotokolls erklärt werden.

TEIL 2: BEWEGUNG UND MULTIMORBIDITÄT IM TÄGLICHEN LEBEN

Der zweite Teil dieser Dissertation konzentriert sich auf die Assoziation zwischen täglicher Freizeitbewegung und Multimorbidität. Nachdem Patienten mit Komorbidität Ihre

physiotherapeutische Behandlung abgeschlossen haben, ist es wichtig dass ein ausreichendes Maß an Bewegung im täglichen Alltag erhalten bleibt. Bezüglich der zunehmenden Anzahl von Patienten mit Multimorbidität versuchten wir herauszufinden, welche Patientengruppen wahrscheinlich Mühe habe sich auch nach Therapieende ausreichend zu bewegen.

Kapitel 6 präsentiert die erste Studie auf dem Gebiet der Multimorbiditätsforschung die einen Zusammenhang zwischen Gruppierungen von chronischen Krankheiten und Freizeitbewegung herstellt. Freizeitbewegung wurde in diesem Zusammenhang binär gemessen als Einhaltung/nicht Einhaltung der niederländischen Bewegungsleitlinie. Diese Leitlinie besagt, dass jeder Erwachsene 30 Minuten oder mehr gemäßigt intensive körperliche Bewegung (3 bis 5 MET) an mindestens fünf, vorzugsweise an allen Tagen der Woche ausführen soll. Wards hierarchisches agglomeratives Clusterverfahren und ein K-Means-Algorithmus wurden auf Querschnittsdaten von 3386 Patienten von der Niederländischen Kohorten Studie für Medizinische Information und Lebensstile in Eindhoven (SMILE Studie) angewandt. Unsere Ergebnisse zeigten, dass die Leitlinienempfehlung für ein ausreichendes Maß an Bewegung am besten von Patienten mit Lebererkrankungen, schweren Rückenproblemen, Rheuma, Arthrose in den Knien, Hüften und Händen und entzündlicher Gelenkserkrankung eingehalten wurde. Patienten mit kardiovaskulären Erkrankungen, chronischen Atemwegserkrankungen und Diabetes Mellitus erfüllten die Bewegungsrichtlinie häufig nicht. Wir schlussfolgerten, das Physiotherapeuten besonders Patienten mit kardiovaskulären Erkrankungen, chronischen Atemwegserkrankungen und Diabetes Mellitus dabei unterstützen sollten ausreichende Bewegung im täglichen Alltag zu realisieren und beizubehalten.

Da die Mehrheit der Patienten mit Multimorbidität an zwei chronischen Erkrankungen zugleich leidet, stellte sich die Frage, welche chronischen Krankheitspaare in welcher Art und Weise mit Bewegungsmangel assoziiert sind. Wir testeten in wie fern die Kombination von zwei Erkrankungen zu noch schlechteren Bewegungsniveaus führt, als das was an Hand der Summe der individuellen Effekte beider Erkrankungen zu erwarten wäre. In Kapitel 7 untersuchten wir die Assoziation zwischen chronischen Krankheitspaaren und der Einhaltung der niederländischen Bewegungsleitlinie. Chi-Quadrat Statistiken wurden verwendet um zu testen, ob eine inverse Assoziation zwischen 105 chronischen Krankheitspaaren und Einhaltung der niederländischen Bewegungsleitlinie vorhanden war. Um die getrennten und gemeinsamen Auswirkungen der Krankheiten auf die Einhaltung der niederländischen Bewegungsleitlinie zu untersuchen haben wir eine logistische Regressionsanalyse durchgeführt. Die folgenden chronischen Krankheitspaare: chronische Atemwegserkrankungen und schwere Rückenprobleme; Migräne und entzündliche Gelenkerkrankung; chronische Atemwegserkrankungen und schwere Nierenerkrankung; chronische Atemwegserkrankungen und entzündliche Gelenkerkrankung; entzündliche Gelenkerkrankungen und Rheuma; und Rheuma und Knie,- Hüft,-

und Handarthrose waren assoziiert mit einer geringeren Umsetzung der Bewegungsleitlinie. Wir konkludierten, dass die Kombination der Krankheiten an dem ein Patient leidet eine wichtige Rolle spielt und dass sich die negativen Effekte von manchen Krankheitskombinationen auf Bewegung gegenseitig verstärken.

Die Ergebnisse der oben beschriebenen Studie lassen vermuten, dass spezifische Kombinationen von Erkrankungen eine Rolle spielen im Zusammenhang von Multimorbidität und Bewegung. Aufgrund dessen beschlossen wir diese Dissertation mit einer innovativen Analyse, sowohl auf dem Forschungsgebiet der Multimorbidität, als auch auf dem Forschungsgebiet der Bewegung zu beenden. Das Ziel von Kapitel 8 war es ein Multimorbiditäts- Bewegungsprofil zu erstellen. Wir führten eine Latente Profilanalyse aus, worin wir sowohl fünfzehn chronische Erkrankungen als auch zehn verschiedenen Bewegungsaktivitäten integrierten. Unsere Ergebnisse zeigten vier verschiedene Multimorbiditäts-Bewegungsprofile. Das erste Profil charakterisiert sich durch eine dominierende Wahrscheinlichkeit für eine chronischen Erkrankung der Atemwege, einer Herzkreislauferkrankung, einer schweren Nierenerkrankung, Diabetes Mellitus, jeglicher Form von Krebs, Epilepsie, Migräne, neurologische Erkrankungen und Schlaganfall, entzündliche Gelenkerkrankung, rheumatoide Arthritis, Arthrose in Knien, Hüfte und Händen, schwere Rückenprobleme, und anhaltende Verletzungen von einem Unfall. Patienten mit einer oder mehrerer dieser Erkrankungen verrichteten moderate körperlicher Aktivität. Die höchste Wahrscheinlichkeit einer schweren Darmerkrankung wurde in Profil eins und zwei entdeckt, jedoch wurde bei Patienten mit schwerer Darmerkrankung im zweiten Profil relativ moderate bis hohe allgemeine körperliche Aktivität gefunden. Ebenso wurde das höchste Niveau an sportlichen Aktivitäten bei diesen Patienten festgestellt. Im dritten Profil waren Patienten mit einer hohen Wahrscheinlichkeit für eine Lebererkrankung oder Leberzirrhose und deren allgemeine körperliche Aktivität im Bereich wandern, Rad fahren, Gartenarbeit, Gelegenheitsarbeiten und Haushalt war am höchsten. Profil vier beschreibt eine relativ gesunde Gruppe mit der niedrigsten körperlichen Aktivität.

Kapitel 9 beschreibt unsere Hauptergebnisse, präsentiert methodische Überlegungen und Empfehlungen für die klinische Praxis und die zukünftige wissenschaftliche Forschung. Die Ergebnisse des ersten Teils dieser Dissertation zeigen deutlich das niederländische Physiotherapie Leitlinien ungenügend thematisieren, wie krankheitsspezifische Leitlinien im Falle von Multimorbidität mit einander integriert werden sollten. Die größte Einschränkung unserer Studie zur Anpassung der krankheitsspezifischen Leitlinien durch den Physiotherapeut bei Claudicatio Patienten mit Komorbidität (Kapitel 3) ist, dass wir die Auswirkungen der Anpassungen auf den Therapiefortschritt nicht messen konnten. Im Gegensatz ist der Therapiefortschritt in unserer Studie beschrieben in Kapitel 4 bekannt, jedoch hatten wir hier keine Informationen über das exakte Behandlungsprotokoll. Wir konnten dennoch feststellen, dass Komorbidität physiotherapeuti-

sche Behandlungserfolge verschlechtert. Zukünftige Forschungsprojekte sollten Anpassungen an Leitlinien und dazugehörige Behandlungsergebnisse messen und in Verbinden bringen. Nur so erhalten wir ein vollständiges Bild über die Auswirkungen von Komorbidität in der täglichen physiotherapeutischen Patientenbehandlung. Wir suggerieren eine prospektive Langzeit Physiotherapie-Kohorten Studie auszuführen worin Physiotherapeuten sowohl ihre Behandlungsanpassungen, als auch ihre Beweggründe für diese Anpassungen sowie die Therapieergebnisse registrieren. Der Stellenwert von umfassenden medizinischen Informationen die in elektronischen Patientenakten gespeichert sind, wird für die Multimorbiditätsforschung in Kapitel 4 und 5 hervorgehoben. Eine leicht zugängliche Patientenakte in welcher alle Informationen von unterschiedlichen Gesundheitsdienstleistern und medizinischen Einrichtungen kombiniert wären, würde die Einschränkungen der Datenverfügbarkeit verbessern. Im letzten Teil dieser Dissertation werden Patientenprofile hervorgehoben die unterschiedliche Krankheitskombinationen mit spezifischen Bewegungsaktivitäten verknüpften.

Bis heute fehlt eine übereinstimmende Meinung für sowohl die Definition als auch die Messung von Komorbidität und Multimorbidität, was unser Verständnis begrenzt und es erschwert Forschungsergebnisse miteinander zu vergleichen. Um den Zusammenhang zwischen Multimorbidität und Bewegung weiter zu erforschen ist es wichtig, dass Multimorbidität objektiv und subjektiv gemessen wird. Für die objektive Beurteilung schlagen wir vor Krankheitsparameter zu messen die durch Bewegung beeinflusst werden. Ein Beispiel für einen solchen Parameter ist HbA1c bei Diabetes Mellitus Patienten. Durch Messungen solcher Parameter ist es möglich die genauen Auswirkungen von Bewegung auf die Krankheitslast zu untersuchen. Zusammen mit den wahrgenommenen Begrenzungen körperlicher Aktivität des Patienten könnte so unser Verständnis hinsichtlich des Zusammenhangs zwischen Multimorbidität und Bewegung erweitert werden. Darüber hinaus ist es wichtig durch Langzeitmessungen den Kausalzusammenhang zwischen Multimorbidität und Bewegung zu ermitteln.

Valorisation
Addendum

INTRODUCTION

In addition to the scientific value that has been presented in chapters 2 to 8, this paragraph highlights the societal and economic value of the present thesis. First, the economic and social relevance of this thesis will be highlighted. Second, the potential of our findings for physical therapists, health policy makers and disease prevention officers will be explained. Third, the innovative character of this thesis will be illustrated. Finally, the actions that we have already taken to disseminate the knowledge gained in this thesis will be described. In this paragraph it will also be indicated into which concrete products, services and activities our results can be translated.

SOCIAL AND ECONOMIC BURDEN OF COMORBIDITY AND MULTIMORBIDITY CAUSED BY PHYSICAL INACTIVITY

The increasing prevalence of comorbidity and multimorbidity has been often reported to be closely linked to advanced age and insufficient physical activity [1-5]. Insufficient physical activity has become a leading risk factor for chronic illness causing one million deaths worldwide (about 10% of the total number of deaths) per year. Furthermore, insufficient physical activity levels have been estimated to globally cause 5% of the burden of coronary artery disease, 7% of diabetes mellitus type two, 9% of breast cancer and 10% of colon cancer [6]. Subsequently, the World Health Organization physical activity strategy for the European Region 2016 to 2025 focuses on physical activity as leading factor in health, with particular attention to the burden of chronic diseases associated with insufficient activity levels and sedentary behaviour [7]. Insufficient physical activity in this context from a national perspective is defined as non-compliance with the corresponding age-specific version of the Dutch physical activity guideline (Nederlandse Norm Gezond Bewegen (NNGB)) [8].

Previous research has shown that regular physical activity plays an important role in the primary and tertiary prevention of multimorbidity [5, 6]. We therefore assume that being physically active may also decrease health care costs in the Netherlands. In this thesis we did not estimate the economic burden of insufficient physical activity in relation to chronic diseases. However, we reviewed the scientific literature and found that 744 million euros per year (2% of the total health care costs in the Netherlands) were attributable to insufficient physical activity levels [9]. Moreover, inadequate physical activity behaviour may also influence the indirect health care costs caused from absenteeism and loss of productivity at work. We found no Dutch study that quantified the indirect costs, however comparable research (in Canada) showed that the costs from loss of productivity that were attributable to insufficient physical activity are the two- to fourfold of the direct health care costs [12].

Furthermore, the social burden of multimorbidity was also not directly studied in this thesis. Results from a study conducted by Mars et al. [13] show that older adults with chronic physical illness characterize social participation with a positive feeling and social contact. However from the literature we also know that advanced age combined with the presence of chronic diseases enhances social isolation [14]. Patients with multimorbidity may feel too sick to go out, resulting in a loss of contact with family and friends. Patient's social contacts are then restricted to those that come to visit them. Physical activity may aid people to renew social contacts. For example, dancing contains physical and social interaction and a degree of cognitive involvement, of which all of these three components are of great importance for the health of older adults [15]. Existing social structures should be used to reach older people in order to encourage them to engage in physical activity. Among others, this could be community centres, faith-based institutions or other social institutions.

As a result of the impact of physical inactivity on the total health care costs in the Netherlands and social loneliness, we encourage health care professionals a) to support patients to engage in or maintain an active lifestyle, b) to educate patients about being physically active as a therapeutic modality and the importance of lifelong physical activity in relation to chronic diseases and c) to routinely prescribe physical activity to their patients and monitor this in accordance with the guidelines provided by the Dutch government [16] and the World Health Organization [17].

TARGET GROUP

The results presented in this thesis are important for everyone, since there is a worldwide trend towards becoming less physically active. In general, it is estimated that one third of all adults living in Europe do not achieve the recommended physical activity levels [18]. Different groups have different needs and challenges related to the promotion of physical activity. In the first part of this thesis, we focused on patients with the index disease intermittent claudication. In this patient group, increasing physical activity and especially walking is the most important lifestyle change and also the main target for treatment. To illustrate, death rates of patients with intermittent claudication who are physically active are one third lower compared to patients with intermittent claudication that are physically inactive [19]. Moreover, physical activity as primary treatment modality for patients with intermittent claudication has shown to be more effective than medication and surgical interventions in increasing maximum walking distance [19, 20]. Furthermore, previous research showed that three months of supervised exercise therapy increases the number of patients that comply with the age-specific minimum recommendation for physical activity in the Netherlands (baseline: 43% and after three months of supervised exercise therapy 63%; p= 0.003) [21]. Therefore, efforts should be

made to enhance physical activity and to implement supervised exercise therapy as routine in the clinical practice of patients with intermittent claudication.

With regards to the population of patients suffering from multimorbidity in general, we showed in the second part of this thesis that it is worthwhile to look at specific subgroups. It seems that specific combinations of chronic diseases (i.e. cardiovascular disease, chronic respiratory disease and diabetes mellitus) are strongly associated with inadequate physical activity behavior (Chapter 6, 7 and 8), although chronic diseases and/or multimorbidity may not be the main obstacle towards physical activity. Synergistic effects of chronic disease pairs on physical activity had been identified for the six chronic disease combinations: chronic respiratory disease and severe back problems; migraine and inflammatory joint disease; chronic respiratory disease and severe kidney disease; chronic respiratory disease and inflammatory joint disease; inflammatory joint disease and rheumatoid arthritis; and rheumatoid arthritis and osteoarthritis of the knees, hips and hands. These results may alert health care professionals on extra low physical activity levels in patients with one of these six chronic disease pairs.

Older adults with specific combinations of chronic diseases, such as cardiovascular disease, chronic respiratory disease and/or diabetes mellitus should seek medical advice before striving to achieve the recommended levels of physical activity. National Dutch physical activity recommendations can be applied to older adults with multimorbidity, however adjustments may be necessary based on exercise capacity, specific health risk or limitation of the individual person. Overall, strong evidence from the American Heart Association demonstrates that older adults who currently do not meet the physical activity recommendation can already gain large benefits by slightly increasing in the duration, frequency and/or intensity of their daily physical activity. Municipalities, communities and employees from fitness centers and people involved in neighborhood initiatives can support physical activity in older adults by offering physical activity programs that are specifically designed for older adults. Existing and new physical activity facilities can especially encourage participation by older adults and the environment should provide opportunities and safe places for walking and/or cycling. Increasingly we see 'movement' gardens 'beweegtuinen' in the outdoor area of Dutch nursing homes or assisted living centers. The purpose of these gardens is to get older adults (more) in motion and a survey showed that older adults are generally very positive about this possibility to be able to 'move' outdoors and that most residents are able to participate in the physical activities on these facilities [22]. As residents of the nursing home are physically active together, they have more and more intensive contact with each other. This additional social aspect showed to have stimulating effects on residents to actively participate in these exercises.

INNOVATIVE ASPECTS

Except for Chapter 2 each study design and/or result presented in this thesis is a novelty. Vignette designs for example have been used in previous physiotherapy research to assess the contemporary state-of-the-art on compliance with physical therapy guidelines in the Netherlands. The results showed moderate adherence rates [23-25]. To our knowledge we were the first that used a vignette design to go one step further and to investigate clinical decision making and deviation from guideline recommendation in case of comorbidity. Regarding research methodologies used, none of the previous studies that examined the influence of demographics and comorbidity on treatment outcome of supervised exercise therapy in patients with intermittent claudication used a multi-level mixed linear regression model to acknowledge that patients received treatment by different physiotherapists (chapter 4). Another fundamental innovative study was conducted in Chapter 5 in which we studied the criticism that randomized controlled trials include too homogeneous samples resulting in poorly generalizable outcomes. To our knowledge, we were the first that determined the degree of patient selection and treatment response in randomized controlled trials, by comparing baseline characteristics of patients, in our case, with intermittent claudication receiving supervised exercise therapy included in clinical trials and patients treated in usual care.

The main novel aspect of the present thesis is that we combined medical research and public health research. Huge amounts of medical research have been previously conducted that focused on patterns of multimorbidity and underlying pathophysiological mechanisms. In contrast, most public health research has been directed towards the numerous health benefits of physical activity to reduce the burden of chronic illness. Only four studies could be found in the literature that assessed the association between the medical phenomenon ‘multimorbidity’ and the public health determinant ‘physical activity’ [3-5, 26]. However, all four used the mere count of chronic diseases to operationalize multimorbidity. We reasonably hypothesized that specific combinations of chronic diseases probably better explain the association with physical activity. Therefore, in chapters 6, 7 and 8 we presented three unique studies that investigated the association between specific combinations of chronic diseases in relation to physical activity. In chapter 7 we added a second original layer to existing multimorbidity research by examining whether the synergistic effects of chronic disease combinations on physical activity. Another shared advantage of all studies presented in chapters 4 to 8 is the large sample size.

TRANSFER OF KNOWLEDGE

Four scientific articles have been published in international scientific journals. Scientific presentations have been given on several national and international conferences and symposia to share our knowledge gained with other researchers and professionals. For instance, we gave a presentation at the PhD symposium of the Jagiellonian University (2012) Krakow, Poland; the symposium of the Public Health Doctoral Network (2013) in Paris, France; the annual conference of the Guidelines International Network (2014) in Melbourne, Australia; the European Epidemiology Congress (2015) in Maastricht, the Netherlands; and the American Congress of Rehabilitation Medicine (2015) in Dallas, Texas.

To spread our newly gained knowledge most efficiently to our research community we published the results presented in chapter 6 and 7 in special issues. These two special issues (one on multimorbidity, one on physical activity) drew together a range of contributions on multimorbidity and physical activity and allowed therefore more in-depth treatment of our topic than is normally possible within a general journal issue. Furthermore, we made strides in advancing essential knowledge to a local, regional audience by secondary publishing of our results in three different languages (Dutch, German and French) in specialist journals (Chapter 2 and 3). These secondary publications enabled us to reach a wider audience and to show our research output in a simplified way to physical therapists and other health care professionals that might implement this knowledge into clinical practice. Moreover, all ClaudicatioNet physical therapists received a newsletter about our Vignette study to inform them about the results and the conclusions or our study and we presented our findings also at the annual symposium of ClaudicatioNet to also give room for discussion related to the results of our Vignette investigation.

Regarding the implementation of our results we are in close contact with the guideline development group of the Royal Dutch Society for Physical Therapy (KNGF). This group translates the latest evidence into clinical practice guidelines. These guidelines are then used by physical therapists as a reference for treating their patients. Our results contribute to the further development and the updating process of internationally available physical therapy guidelines. We highlighted that physical activity levels are worse in patients with cardiovascular disease, chronic respiratory disease, diabetes mellitus type two and that in six chronic disease combinations the risk for low physical activity exceeds what would be expected based on the effects of each of the two diseases alone. For all these disease combinations a warning regarding possible inadequate physical activity behavior could be added to current guidelines. On an international level, the first author of the present thesis is a member of the working group on multimorbidity and allied health of the Guidelines International Network (G-I-N). This working group is a forum where international experts in the field discuss on how multimorbidity can be addressed in guidelines and how we can improve the care of patients with multimorbidity.

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"A simple 'Thank You' would suffice."

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Sarah

About the author

CURRICULUM VITAE

Sarah Dörenkamp was born on March, 10th 1987 in Viersen, Germany.

After graduating from secondary school at the 'Bischöfliche Marienschule privates Gymnasium für Mädchen und Jungen' in Mönchengladbach, Sarah studied Health Sciences at Maastricht University from 2008 to 2011. She followed a major in Human Movement Sciences and a minor in Bioregulation and Health. Next to her Bachelor, Sarah followed a two-year Honours Programme in Education. After graduating from both programs, Sarah continued her education at Maastricht University with a Research Master in Health Sciences. Within the research master Sarah followed the specialization Clinical Epidemiology and obtained her Master's degree in Health Sciences Research (*cum laude*) in 2013. Sarah already started her PhD project at the Department of Epidemiology within the School of Public Health and Primary Care (CAPHRI), during the second year of her master thanks to a prestigious NWO Graduate Programme fund she received for her research proposal on the impact of comorbidities in effective treat-treatments according to clinical guidelines, in open competition from CAPHRI, resulting in the present thesis.

Since 2014 Sarah is registered as Epidemiologist A at the Dutch Society for Epidemiology. In the same year Sarah became a member of the Guidelines International Network. Within this network she is actively involved in the G-I-N working group on multimorbidity. Furthermore, Sarah is part of the congress organization team of the national conference 'Onderzoek in Beweging'.

Besides her education, Sarah was actively involved in student representation. Sarah was a member of the Student Council Health and Life Sciences from 2009 - 2012. During her time as bachelor student, Sarah was first a member of the Educational Committee Health Sciences. Afterwards, Sarah was elected as student member of the Faculty Council of the Faculty of Health, Medicine and Life Sciences and in 2012 Sarah was appointed as Vice-Chair of this Council. Parallel with the start of her master education, Sarah was selected as student advisor to the Board of Directors of the Educational Institute and she continued her representation work during her time as PhD candidate. In 2013 she started as Co-founder of the PhD representation party 'PhDs, Postdocs and Young Scientists'. For the University Council term 2013 - 2015 Sarah was elected as Scientific Staff Representative. Besides her Council membership Sarah was a presidium member of the University Council and for one year the chair of the Research and Educa-

tion Committee of the University Council. On national level Sarah worked as PhD representative for Maastricht University at the National PhD Network (PNN).

Sarah received four academic awards for her work carried out. She was awarded twice for “Best poster presentation“, in 2012 at the national conference ‘Onderzoek in Beweging’ and in 2015 during the European Epidemiology conference ‘Healthy Living’. In 2013 Sarah received a presentation award for the best application of mixed-method approaches at a conference of the Doctoral Network in Paris, France. Moreover, an Education Medal was handed over to her in 2012 as appreciation for her work as student advisor to the Board of Directors of the Faculty of Health, Medicine and Life Sciences.

Since April 2016, Sarah is working as Project manager strategic initiatives at the Research Office at Maastricht University Medical Center.

Über die Autorin

LEBENSLAUF

Sarah Dörenkamp wurde am 10. März 1987 in Viersen, Deutschland geboren.

Nach dem Abitur an der „Bischöflichen Marienschule, Privates Gymnasium für Mädchen und Jungen“ in Mönchengladbach, studierte Sarah Gesundheitswissenschaften an der Universität Maastricht. Als Hauptfach wählte sie Bewegungswissenschaften und als Nebenfach Bioregulation und Gesundheit. Neben ihrem Bachelor nahm sie am zweijährigen Honours Programme in Education Teil. Sarah setzte ihre Ausbildung an der Universität Maastricht mit einem zweijährigen Forschungsmaster in Gesundheitswissenschaften fort. Im Rahmen des Forschungsmasters spezialisierte sich Sarah in der Klinischen Epidemiologie und erhielt ihren Master Abschluss in Health Sciences Research *(cum laude)* im Jahr 2013. Ein Stipendium von der Niederländischen Organisation für Wissenschaftliche Forschung ermöglichte es ihr schon 2012 mit ihrer Doktorarbeit mit dem Titel „Die Auswirkungen von Begleiterkrankungen auf wirksame Behandlungen nach klinischen Leitlinien: Die Tictac Studie“ zu beginnen. Die Ergebnisse ihrer Arbeit als Doktorandin in der Abteilung Epidemiologie werden in diesem Buch präsentiert.

Seit 2014 ist Sarah bei der niederländischen Gesellschaft für Epidemiologie als Epidemiologin A registriert. Außerdem ist Sarah Mitglied im Internationalen Verbund für klinische Leitlinien. Innerhalb des Verbundes ist sie aktiv in der Arbeitsgruppe für Multimorbidität in Leitlinien.

Neben ihrem Studium war Sarah als Studentenvertreterin aktiv. Sarah war Mitglied des Studentenrates Gesundheitswissenschaften und Biomedizin von 2009 bis 2012. Während ihres Bachelors war Sarah zuerst Mitglied des Bildungsausschusses Gesundheitswissenschaften. Danach wurde Sarah als studentisches Mitglied des Fakultätsrats der Faculty of Health, Medicine and Life Sciences gewählt und im Jahr 2012 wurde sie zur stellvertretenden Vorsitzenden dieses Rates ernannt. Parallel mit dem Beginn ihrer Master Ausbildung wurde Sarah als Studentenberaterin des Vorstandes vom Bildungsinstitut der Faculty of Health, Medicine and Life Sciences ausgewählt. Während ihrer Zeit als Doktorandin führte sie ihre außerlehrplanmässige Arbeit fort. Im Jahr 2013 begann sie als Mitgründerin der Doktoranden Vertretungspartei „Doktoranden, Habilitierende und junge Wissenschaftler“. Für die Universitätsratsamtszeit von 2013 bis 2015 wurde Sarah als Vertreterin für die wissenschaftlichen Mitarbeiter gewählt. Neben ihrer Ratsmitgliedschaft, war Sarah eine von sechs Präsidiumsmitgliedern des Universitätsrates und erfüllte für ein Jahr des Vorsitz des Forschungs- und Bildungsausschusses des

Universitätsrates. Auf nationaler Ebene arbeite Sarah als Doktorandenvertreterin der Universität Maastricht im Doktoranden Netzwerk der Niederlande.

Sarah erhielt vier akademische Auszeichnungen für ihre Arbeit. Zweimal wurde sie für wissenschaftliche Poster Präsentationen ausgezeichnet. Im Jahr 2012 auf der nationalen Konferenz „Onderzoek in Beweging“ und im Jahr 2015 auf der europäischen Epidemiologie Konferenz „Healthy Living“. Im Jahr 2013 erhielt Sarah eine Auszeichnung für ihre Präsentation über die Mixed-Methods designs auf einer Konferenz in Paris, Frankreich. Darüber hinaus bekam sie im Jahr 2012 eine Medaille als Anerkennung für ihre Arbeit als Studentenberaterin im Vorstand des Bildungsinstitutes der Faculty of Health, Medicine and Life Sciences übergeben.

Seit April 2016 arbeitet Sarah als Projektleiterin am Forschungsbüro Maastricht University Medical Center.

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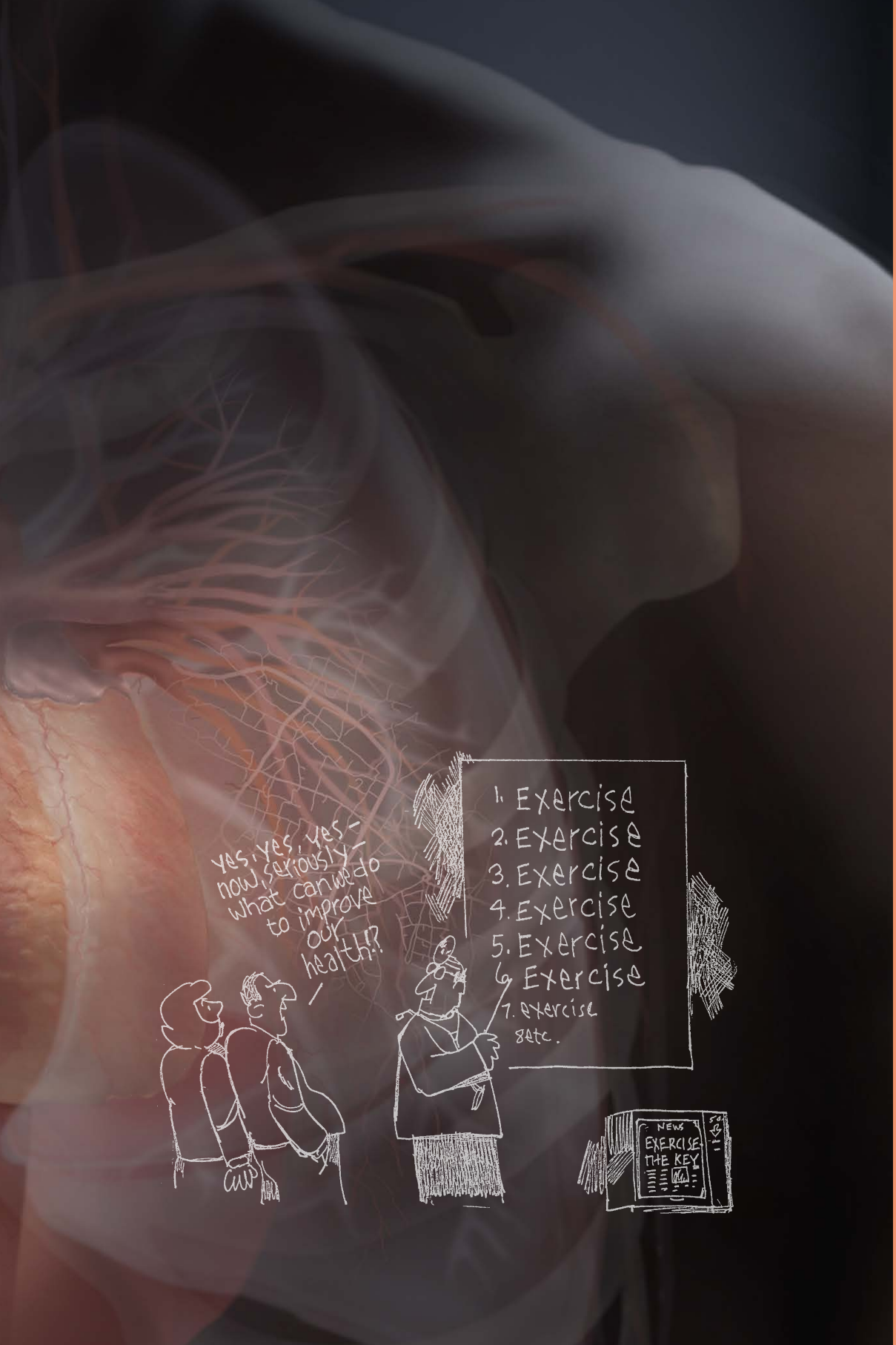
yes, yes, yes- now, seriously- what can we do to improve our health!?
1. Exercise
2. Exercise
3. Exercise
4. Exercise
5. Exercise
6. Exercise
7. exercise &etc.
NEWS
EXERCISE THE KEY