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Combined effects of vitamin D supplementation and progressive resistance training on health-related quality of life and back pain disability among healthy older participants of the NutriAging vitamin D study

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Abstract

Introduction: With an increasing number of elderly persons worldwide, the negative effects of secondary aging in response to an unhealthy lifestyle affect more and more individuals. Lacking physical activity, malnutrition and disorders like back pain lead to a decline in muscle function, higher levels of disability and impaired health-related quality of life (HRQoL). Progressive resistance training (PRT) and vitamin D_3 supplementation are two eligible counter measures to reduce the negative consequences of secondary aging, yet the extent of their symbiotic effects remains unclear.

Objectives: This trial aimed to investigate the changes in muscle function, HRQoL and disability related to back pain in response to a PRT intervention combined with two differently dosed vitamin D_3 supplementation protocols.

Study design: This 16-week study was conducted as a randomized, double blind, placebo-controlled trial and included 100 healthy community-dwelling seniors aged between 65 and 85 years (33% females). Participants were assigned to three supplementation groups: 400 mg calcium per day (CON), 400 mg calcium + 800 IU of vitamin D_3 per day (VDD), 400 mg calcium per day + 50000 IU of vitamin D_3 per month (VDM). The 16-week nutritional intervention started at baseline, while the PRT was only conducted in the last ten weeks of the trial. The self-reported HRQoL (SF-36) and back pain-related disability (RMDQ) were assessed pre- (t1), mid- (t2) and post-intervention (t3). The group differences were determined with the Kruskal-Wallis H test at all time points. Time effects were investigated within each group and the total sample using the Friedman test. The changes observed in the two respective intervention phases from t1 to t2 and from t2 to t3 were compared for each group and the total sample with the Wilcoxon signed-rank test.

Results: Median serum 25(OH)D levels increased significantly in VDD ($p = .002$) and even higher in VDM ($p < .001$). The subjects in VDM showed significant improvements in the median scores of the SF-36 mental component summary (MCS) ($p = .046$) and sub-domain mental health ($p = .015$), but these effects could not be related to one of the intervention phases specifically. The changes in the other scores of the SF-36 were either lacking statistical significance ($p \geq .05$) or could not be attributed to the interventions. The RMDQ scores did not show statistically significant changes ($p \geq .05$) in any of the groups.

Conclusion: These results show the efficacy of the higher vitamin D_3 dose (50000 IU/month) to raise the median vitamin D status from insufficient to sufficient within 16 weeks and provide tentative evidence for its positive effects on the mental HRQoL of seniors. Additional effects might have been expected in response to higher serum 25(OH)D concentrations and/or to a prolonged intervention period.

Zusammenfassung

Einleitung: Ein ungesunder Lebensstil, gekennzeichnet durch Bewegungsmangel und Unterernährung, führt zum frühzeitigen Verlust von körperlicher Funktionalität und in Folge zu niedrigerer Lebensqualität im Alter. Zusätzliche Einschränkungen können durch Erkrankungen wie Rückenschmerzen auftreten. Gesundes Altern wird durch progressives Krafttraining und die Supplementierung von Vitamin D_3 unterstützt, wenngleich deren gemeinsame Wirkung noch wenig erforscht wurde.

Zielsetzung: Diese Studie untersuchte den Einfluss einer kombinierten Krafttrainings- und Ernährungsintervention (Vitamin D_3) auf die Muskelfunktion, Lebensqualität und Behinderung hervorgerufen durch Rückenschmerzen von älteren Personen.

Studiendesign: Eine 16-wöchige randomisierte, doppelblinde und Placebo-kontrollierte Studie wurde mit 100 (33% weiblich) gesunden und selbstständig lebenden Personen im Alter zwischen 65 und 85 Jahren durchgeführt. Die ProbandInnen wurden in drei unterschiedliche Supplementierungsgruppen eingeteilt: täglich 400 mg Kalzium (CON), täglich 400 mg Kalzium + 800 IE Vitamin D_3 (VDD), täglich 400 mg Kalzium + monatlich 50000 IE Vitamin D_3 (VDM). Die Ernährungsintervention lief über die gesamte Studiendauer, während das Krafttraining nur in den letzten zehn Wochen durchgeführt wurde. Zu Studienbeginn (t1), nach 6 Wochen (t2) und am Ende der Studie (t3) wurden mittels Fragebögen die Lebensqualität (SF-36) und funktionellen Einschränkungen durch Rückenschmerzen (RMDQ) erhoben. Gruppenunterschiede wurden zu allen Zeitpunkten mit dem Kruskal-Wallis H Test untersucht. Innerhalb jeder Gruppe wurden die Zeiteffekte durch den Friedman Test überprüft und die Veränderungen der zwei Studienphasen (t1 bis t2, t2 bis t3) wurden mit Hilfe des Wilcoxon-Vorzeichen-Rang Tests verglichen.

Resultate: Die medianen Vitamin D Level stiegen signifikant in VDD ($p = 0,002$) und VDM ($p < 0,001$), mit vermehrten Zuwächsen in VDM. Die Personen in VDM zeigten zusätzlich signifikante Verbesserungen in der mentalen Summenskala ($p = 0,046$) und der Subdomäne „Mentale Gesundheit“ ($p = 0,015$) des SF-36 über die gesamte Studiendauer. Die Veränderungen in den übrigen SF-36 Dimensionen waren entweder insignifikant ($p \geq 0,05$) oder nicht auf eine der Interventionen zurückzuführen. Die funktionellen Einschränkungen, erzeugt durch Rückenschmerz, zeigten keine signifikanten Ergebnisse.

Diskussion: Die höher dosierte Vitamin D_3 Supplementierung (50000 IE/Monat) führte bei SeniorInnen mit einem ursprünglich insuffizienten medianen Vitamin D Niveau zu einer medianen 25(OH)D-Serumkonzentration über 30 ng/ml und des Weiteren zu einer teilweisen Verbesserung der psychischen Lebensqualität. Nach dem Vergleich dieser Ergebnisse mit denen anderer Studien könnten zusätzliche Effekte durch einen höheren Vitamin D Status und/oder eine längere Interventionsdauer erwartet werden.

Table of contents

Abbreviations I

List of tables II

List of figures II

1 Introduction 1

1.1 Aging 1

1.1.1 Physiological effects of aging 2

1.1.2 Mental effects of aging 5

1.1.3 Nutritional aspects and aging 7

1.2 Health-related quality of life 9

1.3 Back pain 10

1.4 Progressive resistance training 11

1.4.1 Training recommendations for the elderly 15

1.4.2 Effects of progressive resistance training on quality of life 16

1.4.3 Effects of progressive resistance training on back pain 17

1.5 Vitamin D 18

1.5.1 Vitamin D metabolism and production 20

1.5.2 Factors influencing the natural vitamin D_3 production 23

1.5.3 Vitamin D supplementation 24

1.5.3.1 Vitamin D level measurement 25

1.5.3.2 Optimal vitamin D levels 25

1.5.3.3 Factors affecting vitamin D supplementation 26

1.5.3.4 Reference Dietary Intake and Tolerable Upper Intake 27

1.5.4 Effects of vitamin D on quality of life 29

1.5.5 Effects of vitamin D on back pain 30

1.6 Overview of combined vitamin D and training interventions 31

1.7 Aims of this study 33

2 Methods 35

2.1 General procedure 35

2.2 Recruiting and inclusion/exclusion criteria 36

2.3 Randomization 37

2.4 Intervention 37

2.4.1 Nutrition 37

2.4.2 Training 38

2.5 Outcomes 41

2.5.1 Anthropometric data 41
2.5.2 Serum 25(OH)D concentrations 42
2.5.3 SF-36 questionnaire – Health-related quality of life 42
2.5.4 Roland & Morris Disability Questionnaire – Back pain 43
2.6 Statistical analysis 43

3 Results 45
3.1 Participant flow 45
3.2 Baseline characteristics 46
3.2.1 Anthropometrics and serum 25(OH)D concentrations 46
3.2.2 Baseline SF-36 scores 47
3.2.3 Baseline Roland & Morris Disability Questionnaire scores 48
3.3 SF-36 physical component summary 49
3.4 SF-36 mental component summary 50
3.5 SF-36 sub-domains 51
3.6 Roland & Morris Disability Questionnaire scores 54
3.7 Blood serum 25(OH)D concentrations 55

4 Discussion 57
4.1 SF-36 scores 57
4.2 Roland & Morris Disability Questionnaire scores 59
4.3 Serum 25(OH)D concentrations 60
4.4 Limitations 63

5 Conclusion 63

Bibliography 64

Abbreviations

$1,25(OH)_2D_3$	1,25-dihydroxyvitamin D_3
1RM	one-repetition maximum
$25(OH)D_3$	25-hydroxyvitamin D_3
5RM	five-repetition maximum
7-DHC	7-dehydrocholesterol
ADL	activities of daily living
BMI	body mass index
CON	the placebo controlled group
CYP	cytochrome P450 mixed-function oxidase
IU	international unit
LBP	low back pain
MCS	mental component summary
MED	minimal erythemal dose
PCS	physical component summary
PRI	population reference intake
PRT	progressive resistance training
RCT	randomised controlled trial
RDA	Recommended Dietary Allowance
RDI	Reference Dietary Intake
RMDQ	Roland-Morris Disability Questionnaire
SF-12	12-item Medical Outcomes Study short-form health survey
SF-36	36-item Medical Outcomes Study short-form health survey
SZA	solar zenith angle
t0	participant assessment
t1	baseline testing and start of the vitamin D_3 intervention
t2	mid-intervention testing and implementation of the PRT
t3	post-intervention testing and stop of both interventions
UL	Tolerable Upper Intake Level
VAS	Visual Analogue Scale
VDD	the vitamin D daily group
VDM	the vitamin D monthly group
VO_2max	maximal oxygen consumption

List of tables

Table 1: Vitamin D nomenclature 20
Table 2: Vitamin D RDIs, ULs and recommended status 28
Table 3: Progressive resistance training intervention exercise pairs 39
Table 4: Exercise starting weights for the first two sessions 39
Table 5: Baseline anthropometrics and serum 25(OH)D concentrations 46
Table 6: Baseline SF-36 scores 47
Table 7: Baseline Roland & Morris Disability Questionnaire scores 48
Table 8: Results SF-36 physical component summary scores 49
Table 9: Results SF-36 mental component summary 50
Table 10: Results SF-36 sub domains 52
Table 11: Results Roland & Morris Disability Questionnaire 54
Table 12: Results serum 25(OH)D concentrations 55

List of figures

Figure 1: Illustration of the vitamin D metabolism. 23
Figure 2: Study design. 36
Figure 3: Training progression. 41
Figure 4: Participant flow. 45
Figure 5: Relative vitamin D status distributions. 56

1 Introduction

This thesis is part of the on-going NutriAging research project, a trans-border initiative between the University of Vienna and the Comenius University of Bratislava, which was funded by the European Union (INTERREG SK-AT). The project aims at the identification of eligible measures to improve the mental and physical health of aging individuals and at raising awareness of a healthy diet and lifestyle, which promote a healthy aging process (Wagner & Muchová, 2020). Facing a rising share of older persons in the global population (United Nations, 2020), healthy aging is a subject of increasing importance for seniors, future seniors and individuals and institutions involved in the care of the elderly alike.

Aging is a complex and multidimensional process and holds manifold implications for maturing individuals, since it can simultaneously affect their physical, mental, social and emotional health (Kadariya et al., 2019).

1.1 Aging

Societies are getting older all around the globe. In 2020, there were an estimated 727 million persons aged 65 years or older worldwide, representing 9.3% of the global population. Their number is projected to more than double by 2050, resulting in over 1.5 billion elderly persons and increasing their share in in the global population to 16% (United Nations, 2020). At the beginning of 2020, the share of Austrian residents older than 65 years was already 18.9 % and on average, women died at the age of 84.2 years and men when aged 79.5 years (Statistik Austria, 2021).

Although this can be seen as a testimony to the recent advances in medicine, science and technology, it also implies that more individuals are confronted with a plurality of age-related transformations on a physical, mental and social level, which eventually lead to severe disabilities (Sieck, 2018). Rising life expectancies in tandem with low birth rates in developed countries (Cursaru, 2018), led to high shares of seniors living alone in these regions (United Nations, 2020). These living arrangements limit social support through friends and relatives in the completion of the activities of daily living (ADL) and pose threats to the emotional well-being of elderly persons (You & Lee, 2006). A healthy lifestyle is crucial to maintain high levels of independence and quality of life into old age, which can be diminished through institutionalization (De Medeiros et al., 2020).

Although the inevitable biological decline of the human body and mind can never be completely averted, the aging process can be positively influenced by physical activity (Bauman et al., 2016) and a healthy diet (Leslie & Hankey, 2015). Seniors are exposed to

an elevated risk of malnutrition with increasing age (Watson et al., 2006) and represent the least physically active age group (Chodzko-Zajko et al., 2009).
Before looking into possible measures to initiate healthy aging and to preserve seniors' quality of life, some changes on a physiological, mental and nutritional level, commonly occurring within the aging process, are summarized in the following chapters.

1.1.1 Physiological effects of aging

The complex physiological processes of aging can generally be related to primary or secondary aging, an established differentiation encountered in literature (Anstey et al., 1993). Primary aging refers to the inevitable and naturally arising biological mechanisms of aging, whereas secondary aging includes environmental and behavioural influences and is caused by external factors, such as diseases or lifestyle. Both forms of aging are associated with numerous transformations of cells, organs or the whole body systems and can generally be categorized based on these three levels (Young & Maguire, 2019).

- The first domain covers changes in cellular homeostatic processes, influencing factors such as body fluid volumes or thermoregulation.
- The second dimension includes the decrease of organs in mass, as well as their structural remodelling.
- The third level relates to the continuous decline of body system functionality (Dodds, 2006).

Changes in subcellular processes, such as impaired receptor activity, are influenced by genetic factors and associated with disorders like dementia, late life depression or the reduction of autonomic regulatory capacities. Stem cells lose their capability of specialization with increasing age, rendering certain cell damages (i.e. muscle) irreversible without transfusion (Young & Maguire, 2019). Other phenomena originating from cellular levels, but showing apparent effects are shifts in the hormonal balance, causing for instance the reduction and lastly the loss of the reproductive capacity (Sieck, 2018).
Age-related transformations of organs can be observed throughout the human body. Heart and lungs both lose efficiency due to structural and regulatory changes, leading to decreased cardiac output and maximal oxygen consumption (VO_2max); latter is estimated to fall by 10% per decade (Siparsky et al., 2014). Tissue degradation and declined enzymatic activity occur in the liver and kidneys and their reduced functionalities relate to symptoms such as clotting disorders and impaired blood purification or bladder and urinary conditions respectively (Dodds, 2006).
All these physiological changes hold implications for a person's life, yet some of the impacts might be alleviated by behavioural adaptions, at least temporarily. It is only when

elderly people can no longer compensate for these age-inflicted impairments that their physical decline turns into a perceivable disability. In many cases one of the first reductions in functionality is observed in connection with the locomotive system, since the decline in musculoskeletal health starts short after adolescence (Knight et al., 2017).

Peak bone mass and density are reached in the early 20s of a person's life and natural bone loss begins around the mid 30s (Teegarden et al., 2009). From the third decade onwards cortical bone will diminish by 20 – 35% and trabecular bone by 30 – 50% over the lifetime, while women generally experience larger relative losses than men (Hunter et al., 2000). Worldwide, the main causes for pathological levels of bone strength and mass are osteoporosis and its precursor osteopenia (Sözen et al., 2017) with high prevalence especially among the elderly and in developed countries (Johnell & Kanis, 2007). These diseases are defined as a pathologic reduction in bone mass and a weakening of its structural architecture. This deterioration of bone quality increases the risk of fractures, which subsequently often lead to lasting disability and to impaired quality of life among older and frail individuals (Sözen et al., 2017).

The term frailty is often used in connection with musculoskeletal conditions and age-induced physical decline, yet it is still lacking an internationally standardized definition. A large diversity of associated phenotypes and symptoms can be observed in literature as well as different opinions on the exclusive use for older populations (Dent et al., 2016). It can be seen as a multidimensional condition, characterized by reduced resistance against external stressors, and it relates to functional, structural and mental disorders (Landi et al., 2015). Dent et al. (2016) tried to shed light on the controversy about frailty measures and identified Rockwood and Mitnitski's Frailty Index (Mitnitski et al., 2001) and Fried's frailty phenotype (Fried et al., 2001) as the two most common quantification instruments, as both offer high validity and reliability. Latter was also included in the participant assessment of the present trial. Further, frailty can be caused by the loss of muscle mass and strength. The annual decline in muscle mass is estimated as high as 1 - 2%, starting at the age of 35 years, and is accompanied with an annual decrease in strength of 1.5%, which accelerates up to 3% in individuals aged 60 years and older (Landi et al., 2015). Though this prediction appears quite excessive compared to a previously suggested annual decline in muscle mass of 0.2 - 0.5% after the fifth decade (Kyle et al., 2001).

The term sarcopenia originally described the natural loss of muscle mass, but is now defined as a disorder and no longer restricted to the aging process only (Alfons J Cruz-Jentoft & Sayer, 2019). Cruz-Jentoft and Sayer (2019) emphasise its new recognition as a muscular disease, characterized with low muscle function, quantity and quality. They further elucidate, that factors relating to muscle function, such as muscle strength, muscle power or physical performance, had been included in this revised definition. These

functional parameters offer higher clinical value than muscle mass alone: As described before, muscle strength declines at a higher rate than mass (Landi et al., 2015). Muscle power has emerged as a even better predictor of muscle function (Reid & Fielding, 2012), since it also considers movement velocities and is therefore associated with a twofold deterioration over muscle strength (McKinnon et al., 2017).

Estimates of worldwide prevalence for sarcopenia range from 11.1% to 20.2% and the number of patients is projected to rise drastically until 2045 (Reginster et al., 2017). It is related to a broad range of adverse health outcomes including falling, impaired muscle function, lower quality of life and frailty (Alfonso J Cruz-Jentoft et al., 2019). The clinical pictures of frailty and sarcopenia show a large overlap, especially when focussing on the physical dimension of frailty. Determining the exact causal relationship between these two disorders is challenging and led to a rather pointless controversy in consideration of the continuous refining of their definitions (Landi et al., 2015).

Regarding changes in body-composition with age, relative fat mass is increasing, especially in the abdominal area, while muscle tissue is declining (St-Onge & Gallagher, 2010), yet the exact mechanisms behind this process are still discussed. Most likely the decline in muscle tissue is related to a decrease in size and quantity of muscle fibres (Mcphee et al., 2018), even though some research disclaims substantial fibre-loss and mainly relates these changes to the atrophy of fast-twitching type II fibres (Nilwik et al., 2013). However, the age-related changes observed in connection with the human muscle cannot be cut down on quantitative aspects only, but are rather multidimensional.

On average, the muscle tissue of older individuals shows lower quality, due to increased structural stiffness, fat-infiltration, reduced specific tension and prolonged myosin cross-bridge cycles, which are responsible for muscle contraction and relaxation (Vandervoort, 2002). Filaments of myosin, a motor enzyme, pull on filaments made of actin, another protein, to generate power and subsequently release their grip to return into a resting position (Kronert et al., 2018). These muscular processes are getting slower and produce less power with increasing age, mainly due to the reduced number of myosin filaments (Deschenes, 2004), but efficiency is also impaired by diminished neurological innervation (Miller et al., 2013).

There are different isoforms of myosin expressed in type I and type II muscle fibres, yet later in life the augmented co-expression of both isoforms can be observed, decreasing the homogeneity of muscle fibres (Larsson et al., 2019). This missing homogeneity is one of the reasons for the higher functional limitation of type II fibres compared to slow-twitching type I fibres in the mature muscle. As a result, elderly subjects show high restrictions in the generation of short-term peak forces, needed for concentric movements such as climbing stairs or getting up (Vandervoort, 2002).

Another mechanism on the bottom of muscular decline is the remodelling of the motor unit with increasing age. The term motor unit refers to muscle fibres and their respective motoneurons and while their numbers decline throughout life, the size of the still remaining motor units is growing (Brown, 1972). Motor units are lost due to impaired regeneration of neural tissue, which is more prevalent in the pool of type II fibres (Larsson et al., 2019). Some of these inertial units are re-innervated by still active motoneurons of slow-twitching fibres by collateral sprouting and cause a predominance of type I functionality over type II in the elderly (Siparsky et al., 2014).

All of these musculoskeletal changes influence the functionality of the locomotive system, whose impairment holds significant implications for the every-day life and well-being of older adults. High muscle strength and mass are established indicators for good physical performance among the elderly (Bao et al., 2020). Yet as mentioned before, muscle power was repeatedly identified as an even better predictor in this context (McKinnon et al., 2017; Reid & Fielding, 2012), especially considering the age-related reduction in type II fibre efficiency (Larsson et al., 2019). The maintenance of functional performance proved vital for lasting mobility (Bean et al., 2013) and the successful completion of ADL (Wang et al., 2020), both essential to ensure independence up until old age (Fragala et al., 2019). Good musculoskeletal function is further associated with high levels of health-related quality of life (HRQoL), positive overall health status, reduced need for institutional care and lower risk of fractures (Kell et al., 2001).

1.1.2 Mental effects of aging

Apart from changes manifesting on the physical level, aging is also associated with numerous mental effects. The differentiation of adverse and normal mental aging processes seems even more challenging compared to the bodily domain.

Looking at cognitive functions a natural decline in memory, attention, visuospatial ability and information processing speed of the human brain is generally observed with increasing age (Mendoza-Ruvalcaba et al., 2018). Although the exact mechanisms responsible for decreasing cognitive reserves are not fully clarified, this degradation can be mostly related to physiological changes within the human brain (Manor & Lipsitz, 2013). The identification and assessment of valid parameters in this context pose a challenge for further research. As we know so far, age-related cognitive changes are associated with the synaptic decline in number and functionality (Young & Maguire, 2019), the decrease of grey matter and impaired cerebral blood flow (Steffener et al., 2013). Apart from the physiological influences, cognitive performance in advanced age is also related to behavioural parameters (Barnes et al., 2007). Different longitudinal studies linked the maintenance of good cognitive functions to factors such as weekly exercise

(Yaffe et al., 2009), subjective health (Habib et al., 2007) and successful completion of ADL (Barnes et al., 2007). The relation between cognitive and physical performance, implied by the aforementioned associations, was observed before among elderly persons when linking better results in cognitive measures to higher gait speed (Rosano et al., 2005). Further, the functional muscle parameters strength (Frith & Loprinzi, 2018) and mass (Low et al., 2020) had also been related to cognitive function, while muscle strength was identified as the more reliable indicator for good cognitive function at an advanced age (Sui et al., 2020). Sui et al. (2021) provided tentative evidence linking the decline in cognitive function to sarcopenia, as both conditions might share the same pathophysiological pathways. However, more research is needed to relate specific traits of the multidimensional phenotype associated with sarcopenia to decreasing cognitive performance (Sui et al., 2021). Another indicator for a possible physiological relation of cognitive function and sarcopenia can hypothesised with the shared response to vitamin D supplementation: For one vitamin D was able to alleviating the negative consequences of sarcopenia (Uchitomi et al., 2020). Additionally, cognitive performance was successfully preserved with the oral administration of vitamin D in older females (Beauchet et al., 2019). It should be mentioned, that the randomized controlled trial (RCT) of Beauchet et al. (2019) only included a very small study sample (n = 40) and showed a short intervention period (3 months).

As stated before, these conclusions are rather speculative. Nevertheless, further research on the effects of vitamin D on sarcopenia and cognitive function could result in a simple and cost-efficient measure to alleviate two severe age-related disorders simultaneously. Though there are other factors more frequently observed to preserve good cognitive function, they are harder to influence: high social participation (Barnes et al., 2007; Josefsson et al., 2012), good education (Habib et al., 2007; Yaffe et al., 2009) and favourable genetics (Josefsson et al., 2012; Yaffe et al., 2009).

Further, reduced cognitive function with increasing age is associated with some adverse mental disorders, such as late life depression, a condition originating from physiological and hormonal dysfunctions, which can also occur in response to medication (Fiske et al., 2009). Fiske et al. (2009) state, that depression severely impedes mental and physical health and renders patients more depended and increased socially vulnerable, compared to healthy persons. Older subjects with impaired physical function are more likely to experience depressive symptoms than healthy individuals: depression was associated with muscle strength, balance and walking speed (Kvæl et al., 2017). Further prospective research is needed to identify a possible relation to other functional muscle parameters (i.e. muscle power) and to evaluate their eligibility for the detection, prevention and treatment of late life depression. Vitamin D might again serve as an easy intervention

measure to relieve depressive symptoms in older persons. In contrast to the direct association with cognitive function, the scientific evidence for the mitigating effects of vitamin D on depression is more substantial, yet good results have mainly been reported in elderly subjects showing low vitamin D status (Alavi et al., 2019; Mozaffari-Khosravi et al., 2013; Sepehrmanesh et al., 2016). A review on the potential effects of vitamin D on late life depression included mostly trials with replete participants and also reported better results among vitamin D deficient subjects (Rejnmark et al., 2017).

Cognitive and executive functions were also impaired in elderly individuals living alone, when compared to persons living with relatives (You & Lee, 2006). Latter also reported better physical and emotional health, highlighting the multidimensionality of HRQoL. The maintenance of independence as well as of social roles and activities are among the most important aspects bringing quality to the lives of seniors (Bowling et al., 2003). Without proper physical and cognitive function, these meaningful areas of late life are endangered. Missing social embedment limits potential support and severely threatens HRQoL in older adults (Vanleerberghe & Verte, 2017) and can even be a risk factor for malnutrition (Leslie & Hankey, 2015).

1.1.3 Nutritional aspects and aging

The aging process is often accompanied with a shortfall in nutrients and the loss of overall body mass, commonly referred to as anorexia of aging. The term anorexia of aging sums up manifold factors causing poor nutritional status in older adults: social factors, chronic illness and physiological changes with age are the most common causes for these adverse changes in dietary practice (Leslie & Hankey, 2015).

Leslie and Hanky (2015) elucidate, that many elderly persons grow less concerned about their nutritional health with increasing age. They tend to cook proper meals less frequently and rather consume snacks. Eating healthy might become negligible in the face of emotional resentment or social isolation, due to the missing gratification of a shared meal. Even if the diet remains an important aspect in an individual's life, older people can be limited by their economic status or physical health in provisioning and preparing fresh foods with high nutritional content.

Reduced appetite is another common phenomena observed with increasing age, often related to chronic disorders, long-term medication, sensory deprivation (loss of taste and smell) and prolonged gastric emptying (Parker & Chapman, 2004). Poor dentation and dry mouth (xerostomia) impair ingestion and often lead to avoidance of certain aliments with increasing preference of soft and moist foods (Watson et al., 2006).

The decrease of lean body mass lowers the basal metabolic rate by approximately 15% between the third and eighth decade. A slower metabolism in tandem with reduced

physical activity diminishes energy requirements (calories) and generally results in smaller volumes of consumed food (Leslie & Hankey, 2015).

All of these described factors are associated with reduced food intake, exposing older adults to a high risk of micronutrient deficiencies. The maintenance of a healthy nutritional status is further impeded by the commonly observed malabsorption of essential nutrients among the elderly, often related to gastrointestinal disorders such as atrophic gastritis (Watson et al., 2006).

In contrast to the lower caloric demand, the estimated average need for micronutrients, such as vitamin D and calcium, remain the same throughout adulthood. Those necessary levels are met by only few older persons (Kehoe et al., 2019). The Austrian nutrition report (Elmadfa et al., 2012) assessed the nutritional population reference intake (PRI) of citizens aged between 65 and 80 years. Persons in this age range showed a 20% prevalence of severe vitamin D deficiency (< 10 ng/ml) (Amrein et al., 2020) and a PRI for calcium (662 mg/day) below the threshold (950 mg/day) recommended by the European Food Safety Authority (EFSA, 2015). Vitamin D and calcium are both vital nutrients to maintain good musculoskeletal health and functionality in older adults (Kehoe et al., 2019).

Although reduced food intake challenges the maintenance of a good nutritional status, the issue cannot be limited to the quantity of consumed food only, since the nutrient uptake also highly relates to food-quality. Inadequacies of vitamin C, calcium, vitamin D, folate, zinc and magnesium were observed together with a high prevalence of overweight (70%) in community-dwelling seniors, indicating a diet with high energy but low micronutrient content for these individuals (Power et al., 2014).

In general, malnutrition comes along with serious health consequences, such as increased risks of sarcopenia, frailty, falls and mortality, as well as poor wound healing and low quality of life. Compared to healthy persons, individuals with nutritional shortfalls are more depended in their activities of daily living and are hospitalized more frequently and for longer durations, which also imposes severe implications for society and health care services (Roberts et al., 2019).

Even though the administration of micronutrients via fortified food or oral supplementation proved as an effective counter measure against many adverse outcomes of under-nutrition (Kehoe et al., 2019; Leslie & Hankey, 2015; Watson et al., 2006), research on its effects on patient-relevant parameters such as functionality and quality of life is still sparse (Volkert et al., 2019).

1.2 Health-related quality of life

The perceived impairments due to adverse physical and mental function, in addition with social aspects, can be summarized with the parameter of HRQoL. The terms HRQoL and quality of life will be used synonymously in this thesis, although they generally refer to different parameters, since latter is also associated with other influential factors, such as spirituality, material goods, sexual relationships or perceptions of the future and the own body (Carr & Higginson, 2001). HRQoL can be seen as a multidimensional concept, evaluating a person's physical and mental health status in tandem with its social and emotional well-being. Most of the time HRQoL is a self-reported parameter, since it is a measure of the subjective perception and rating of the aforementioned domains. Traditionally, HRQoL assesses the severity of impairments along with their implications on the four primary dimensions physical, functional, social and emotional well-being (Cella, 1994).

According to Cella (1994), physical well-being includes the general health status and negative effects of disorders as well as of their treatments, such as pain, vertigo, fatigue and nausea. The functional dimension represents the individual ability to complete tasks necessary to life up to working requirements, social roles, personal needs and ambitions. Basics in the context of functionality are walking, dressing and feeding. Emotional well-being reflects subjective affections, sentiments and levels of distress. The social domain relates to a person's ability to maintain relationships with family and friends and participate in social and leisure-time activities (Cella, 1994).

These four fundamental dimensions have been refined in recent years, due to apparent changes in society and health care. A standardized definition of HRQoL has not yet been established, even though there is consensus on three main characteristics: quality of life is multidimensional, dynamic and includes objective and subjective parameters (Vanleerberghe & Verte, 2017).

Only about 30 years ago, the absence of a holistic and humanitarian scientific parameter in medical research was frequently criticised (Fallowfield, 1990). The variable HRQoL was created to fill this gap and investigate health from a patient's perspective. Quality of life research is increasing and several publications in recent years cover various areas, including HRQoL related to aging (Hart & Buck, 2019) and to LBP (Mutubuki et al., 2020). However, there is long-standing concern that widely used HRQoL measures not really assess quality of life, since they mainly focus on the physical domain, are lacking a conceptual foundation and are not patient-centred (Carr & Higginson, 2001). The appeal to address these inadequacies led to the development of numerous new questionnaires and a high variety of HRQoL assessment among the elderly in literature (Evans, 2010). Researchers often have to choose between the use of an eligible HRQoL measure for

their trial and the adequate level of comparability with previous studies in their specific field.

A widespread generic HRQoL measure is the 36-item Medical Outcomes Study short-form health survey (SF-36) (Ware & Sherbourne, 1992) and its shorter form, which only contains 12 instead of 36 items (SF-12). The SF-36 assesses eight dimensions. Four of them are related to mental health (vitality, social functioning, role emotional and mental health), while three others are associated with the physical domain (physical functioning, role physical, bodily pain). General health is the eighth domain and relates to physical and mental aspects alike. Two higher-order summary scores can be derived from the eight sub-scores, the physical component summary (PCS) score, representing the bodily domain, and the mental component summary (MCS) score, reflecting psychological aspects.

Looking into previously observed associations between the HRQoL of elderly individuals and factors of the aging process, the multidimensionality of this parameter becomes apparent. High levels of mental, physical and social HRQoL among older individuals were repeatedly indicated by increased muscle strength and mass (Haraldstad et al., 2017; Laudisio et al., 2020; Trombetti et al., 2016). These indications are comprehensible since improvements in these two functional parameters along with good physical performance often lead to better mobility (Bean et al., 2013; Fatouros et al., 2005) and higher success in the completion of ADL in seniors (H. M. Chen & Chen, 2017; Wang et al., 2020). Mobile seniors, who are capable to fulfil the tasks of every-day life, are more likely to engage in social activities, which was already described before as one of the main self-reported factors brining quality into their lives (Bowling et al., 2003) and is also frequently reflected by better scores in generic HRQoL measures (Davis et al., 2015; Haider et al., 2016; Yaya et al., 2020). Disorders in connection with the psychological aging process, such as depression, anxiety or impaired cognitive function hold implications on both, the mental and physical domains of HRQoL (Brett et al., 2019)

Back pain is another disorder strongly associated with increasing age (Hoy, March, et al., 2014) and is also related to the HRQoL of seniors (Cedraschi et al., 2016).

1.3 Back pain

Back pain, or low back pain (LBP), is a widespread disorder showing one of the highest prevalence of diseases worldwide and was repeatedly linked to HRQoL (Carroll & Cassidy, 2015; Horng et al., 2005; Mutubuki et al., 2020).

An astonishing 70 – 85% of the global population suffer from LBP at some point in their life and 90% of patients will even have repeated episodes (Souza et al., 2019). In 2010, it was the leading condition causing disability, activity limitation and work absence in most

parts of the world, inflicting substantial individual and economic burden (Hoy, March, et al., 2014).

The relation between work and back pain is two-sided and hard labour or extensive sitting often causes LBP. Working adults commonly suffer from LBP and its prevalence was believed to decrease after retirement for quite some time. Some researchers expressed their doubts on this hypothesis early on, emphasising the strong association of LBP and musculoskeletal disorders, which generally increase with age (Dionne et al., 2006). Today we know that the burden and prevalence of LBP rise with throughout the lifetime and are at their highest among elderly individuals (Hoy, March, et al., 2014), causing drastic limitations of functionality and well-being (Souza et al., 2019).

Opinions and statistics on the etiologies and risk factors of LBP differ widely, yet most cases of back pain are attributed to mechanical causes or are labelled as unspecific (Casiano et al., 2021). Of all reported incidents, estimates on the share of patients suffering from neuropathic pain are commonly around 5%, but are also reported as high as 55% (Baron et al., 2016).

Regardless of origin, back pain is associated with all dimensions of HRQoL (Carroll & Cassidy, 2015; Horng et al., 2005). Higher reductions are observed in response to the experience of functional disability than of pain alone (Mutubuki et al., 2020), since limitations in functionality hold more implications on the activities of everyday life.

Considering the aging societies around the globe and the high prevalence of LBP observed among older individuals, the global burden of back pain is projected to further increase in the future (Hoy, Geere, et al., 2014). The identification of effective counter measures is necessary to reduce the personal and economic damage caused by LBP in the years to come.

1.4 Progressive resistance training

The increasing worldwide share of older individuals creates the urge to identify eligible strategies to minimize the negative consequences of the aging process. Ideally, these measures do not only alleviate but also avert adverse health outcomes by inducing a healthy aging process.

Since elderly persons represent the least physically active age group and a sedentary lifestyle is one of the biggest risk factors for many negative effects of aging (Chodzko-Zajko et al., 2009), progressive resistance training (PRT) can be a key measure to achieve both, the mitigation and prevention of age related disorders. Generally, the regularity of physical activity is essential to slow down the multidimensional changes of aging, since advantageous influences are fading if remaining inactive, even after a long training period (Beckwée et al., 2019). Additional health benefits are obtained by engaging

in whole body strength exercises twice a week. Regarding older adults in specific, the weekly routine should include a multicomponent program, targeting muscle strength, balance and aerobic capacity (Chodzko-Zajko et al., 2009). Resistance training and PRT in particular have emerged as effective training interventions covering these recommendations for older individuals.

PRT is not a multicomponent program per se, since it is primary designed to increase muscle strength, by gradually advancing the weight-induced resistances. However most PRT regimes include endurance, balance and flexibility exercises in their warm-up and/or cool-down sessions as suggested by guidelines for older individuals (Chodzko-Zajko et al., 2009; McDermott & Mernitz, 2004).

Additionally, the autonomous benefits of PRT on fitness, balance and mobility in older persons are promising and well documented (Bird et al., 2009; Fatouros et al., 2005; Fragala et al., 2019; G. R. Hunter et al., 2004; Liu & Latham, 2011; Papa et al., 2017). The review of Liu & Latham (2011) ascribed endurance training and PRT the same beneficial effects on aerobic capacity. These results are in line with findings of another review examining slightly younger subjects (Hollings et al., 2017). The combination of aerobic and resistance training even showed greater increases in the endurance performance of older individuals than the same extent of aerobic or strength exercises alone. This combination also created more favourable outcomes in balance when compared to a mixed endurance-balance training (G. R. Hunter et al., 2004). PRT and flexibility training were equally effective in improving balance in older healthy adults, while only PRT resulted in strength gains (Bird et al., 2009).

Therefore, PRT is proven to effectively increase balance and aerobic capacity and is most notably the best of the aforementioned training methods to enhance muscle functionality through gains in muscle mass, strength and power (Beckwée et al., 2019; McKinnon et al., 2017). The mature muscle is still able to benefit from adaptations, which cause the increases in these functional parameters (Vandervoort, 2002). Significant improvements in functional performance can even be achieved in subjects over 90 years of age (Papa et al., 2017). PRT creates adequate stimuli needed to set these changes in motion (Vandervoort, 2002), which are usually not provided by certain other types of physical activity, such as flexibility training (Bird et al., 2009).

Increases in functional parameters are not entirely related to muscle hypertrophy and are also caused by neural factors and the familiarization to training routines. Neural adaptations favouring muscle function include increased recruitment of motor units and enhanced innervation of agonists in tandem with reduced antagonist co-contractions (Kosek et al., 2006). Older persons seem to rely more on neural adaptations to improve functionality than younger subjects. Similar strength-gains in all age groups were

accompanied with less muscle hypertrophy in the elderly individuals (Kosek et al., 2006). Relating improvements to familiarization might be important in the assessment of baseline parameters, since excessive benefits, not related to the respective intervention, could be detected by the outcome measures.

A shift in muscle fibre distribution is another non-muscle-mass response to PRT. Fast twitching type II fibres can be further divided into IIa and IIx (or IIb) fibres. Latter show slightly faster contraction velocities than type IIa fibres. PRT was repeatedly reported to favour the expression of slower type IIa fibres, while down-regulating IIx fibres expression in older subjects (Hikida et al., 2000; Kosek et al., 2006), a theoretically unfavourable process for muscle power. However, the hypertrophy and increased numbers of type IIa fibres still cause improvements in muscle power and more than outweigh the small detrimental effect of the changed myosin expression (J. L. Andersen & Aagaard, 2010). Interestingly, an elevated expression of type IIx fibres after the cessation of PRT was observed in different samples (J. L. Andersen & Aagaard, 2000; L. L. Andersen et al., 2005). The changes in the percentage of type IIx fibres in response to a resistance training intervention were investigated among young men. Compared to baseline measurement, the share of type IIx fibres was nearly twice as high after three months of PRT and three additional months of subsequent detraining, although initially decreasing in response to the training (J. L. Andersen & Aagaard, 2000). These findings provide tentative evidence that PRT offers a certain time buffer before muscle power returns to its pre-intervention level after individuals returned to a sedentary state, created by the compensational effect of extra type IIx fibres. Similar results were observed for older adults (Blocquiaux et al., 2020). PRT-induced gains in muscle strength and power were reported to remain partially preserved after 12 weeks of detraining and subjects showed a fast recovery of their one repetition maximum (1RM), after entering retraining.

The favourable effects on various physiological parameters position PRT as a compact method to induce and maintain a healthy aging process. There is substantial scientific evidence, that PRT significantly increases muscle function (strength, power, mass), mobility (balance, flexibility) and physical performance (aerobic capacity, endurance) in older adults (Beckwée et al., 2019; Bird et al., 2009; Fatouros et al., 2005; Fragala et al., 2019; Hunter et al., 2004; Liu & Latham, 2011; Papa et al., 2017; Raymond et al., 2013). The observed beneficial effects of the aforementioned trials will be pooled in similar results and are presented in the following passage.

PRT causes higher levels of independence and confidence by reducing the risk and fear of falling and by mitigating difficulties encountered in the completion of everyday activities, which was proven by various studies (Bird et al., 2009; Fragala et al., 2019; Trombetti et al., 2016). It improves gait speed, walking endurance, stair climbing power and alleviates

getting up and sitting down (Liu & Latham, 2011; Papa et al., 2017; Van Abbema et al., 2015). Favourable shifts in body composition (less fat, more muscle), enhanced energy expenditure and increased appetite are further advantages of regular engagement in PRT (Hunter et al., 2004; Jafari et al., 2017). Resistance training was proven effective to counter adverse muscular effects of hospitalization (Fragala et al., 2019; Sullivan et al., 2001) and is even suggested to decrease the likelihood of hospital admission (Latham et al., 2004). PRT lowers the risk to contract various disorders such as sarcopenia, osteopenia/osteoporosis, frailty, depression and dementia (Beckwée et al., 2019; Fragala et al., 2019; Hollings et al., 2017; Hong & Kim, 2018).

There is also growing evidence on cognitive benefits of PRT among older adults (Li et al., 2018; Voss et al., 2011). The systematic review of Li et al. (2018) reported positive effects on global cognitive function, executive function and small benefits in memory. In another study (Forte et al., 2013) a resistance training intervention significantly improved executive function in elderly subjects by increasing their inhibitory capacity. The beneficial effects of PRT on cognitive function are meditated through the obtained physical improvements and have been ascribed to subsequent hormone and protein expressions favouring cognitive control (Li et al., 2018). Complex exercises might have an additional effect on cognitive function, since challenging movements created neural stimulations enhancing executive functions in older adults (Forte et al., 2013).

Generally, adverse events are rarely observed, when conducting PRT interventions in older individuals, according to four reviews including information on adverse events (Hollings et al., 2017; Latham et al., 2004; Liu & Latham, 2011; Raymond et al., 2013). Serious adverse events (death, events leading to hospitalization) were very rare and none appeared to be directly caused by PRT. However, all of these reviews criticised missing or poor reporting of adverse events in many of the analysed trials. This might have caused an underrepresentation of actual numbers. The provided data positions PRT to be safe for older adults (Hollings et al., 2017), also at higher intensities, since observed adverse events were evenly distributed among low, moderate and high intensity PRT interventions (Raymond et al., 2013). Nevertheless, since many trials did not report adverse events, the conduction of PRT with elderly persons should be conducted under supervision.

Summarizing, PRT can be regarded as a very powerful tool to mitigate many negative effects of aging on physical and mental health, with substantial literature on its efficacy on multiple levels. The broad range of functional benefits reduces the need to engage in several types of training, which facilitates the implementation into a weekly schedule. Improvements are even temporarily preserved after cessation and easily regained when returning to training (Blocquiaux et al., 2020).

1.4.1 Training recommendations for the elderly

As stated above, the conduction of resistance training at all levels of intensity is declared safe among older subjects and is highly recommended. Intensities are depended on external loads, which can be induced in different ways (bodyweight, free weights, resistance machines, elastic bands etc.). The weight resistances and generally based on the one repetition maximum (1RM) and can be categorized as low (< 50% of 1RM), moderate (50 – 69% of 1RM) and high intensity (70 – 89% of 1RM). Higher intensities are considered as maximum resistance training (Raymond et al., 2013).

At slow velocities the use of higher intensities is associated with better improvements in muscle strength, anaerobic power, and physical body function and might preserve improvements for a prolonged period of time after cessation, compared to lower intensities (Fatouros et al., 2005). Additionally these high intensity programs show more beneficial effects on certain disorders, such as sarcopenia, osteoporosis, depression and type 2 diabetes in older adults, according to two independent reviews (Chodzko-Zajko et al., 2009; Hollings et al., 2017). However, high velocity strength training (power training) with lower intensities showed better effects on physical functioning among older subjects than high intensities at slower velocities, especially in activities of lower intensity such as habitual walking (Reid & Fielding, 2012).

Without the explicit need for an initial implementation of high intensity exercises, resistances should be progressed gradually from low/moderate (approximately 50% of 1RM) to high intensities, allowing familiarization and decreasing the risk of injuries (Fragala et al., 2019). Several recommendations (Beckwée et al., 2019; Chodzko-Zajko et al., 2009; Fragala et al., 2019; McDermott & Mernitz, 2004) suggest a total body approach and to perform one to two exercises for every large muscle group. PRT interventions should be conducted for the duration of at least 6 – 12 weeks, with two to three sessions per week, offering 48 hours of rest in between. The number of sets should be increased over time from two to four, including 8 – 15 repetitions per set. Resistances should be increased when subjects are able to complete more than 15 clean repetitions. Warm-up should include exercises raising the heart rate and activating the large muscle groups, while the cool-down routine is recommended to include aspects of flexibility and/or balance training. All trainings should be held under supervision and with constant monitoring of joint stress and soreness. Additional gains in muscle power can be achieved by conducting exercises at higher velocities (power training) with low resistances between 40 and 60% of the 1RM.

1.4.2 Effects of progressive resistance training on quality of life

Beneficial effects of PRT on quality of life among the elderly have been observed previously, although HRQoL is assessed less frequently in exercise intervention trials than functional parameters.

A recent meta-analysis confirmed the effectiveness of PRT to increase HRQoL, including 16 studies with study populations consisting of healthy and clinical older individuals and using SF-36/12 scores as HRQoL outcomes (Hart & Buck, 2019). Improvements in response to PRT were observed in three mental and three physical HRQoL dimensions compared to controls. No significant differences were observed in the sub-domains physical role functioning, emotional role functioning and social functioning.

Further meta-analyses on older subjects suffering from specific disorders, such as cancer (Cramp et al., 2010), chronic heart failure (Giuliano et al., 2017), chronic kidney diseases (Cheema et al., 2014) or rheumatic diseases (Sieczkowska et al., 2020) also proved the favourable influence of PRT on HRQoL. These four reviews assessed data from different HRQoL measures and either pooled the results into subdomains or did not give information on sub-scores.

Sieczkowska et al. (2020) proved PRT to significantly increase overall HRQoL compared to controls, but did not find any differences in comparison to other types of exercise. Among others, they reported improvements in the domains physical functioning, physical role functioning and social aspects contrasting controls. They did not find any differences in vitality, mental health, general health and role emotional in this comparison. Although all of the aforementioned reviews support the positive effects of PRT on HRQoL, the results of the respective sub-domains are diverging and of limited comparability.

Looking into reviews, which do not focus exclusively on PRT, but which investigate the general effects of exercise among older persons and included PRT interventions in their analysis showed benefits in quality of life in response to physical activity (Bauman et al., 2016; Gillison et al., 2009; Schechtman & Ory, 2001; Vagetti et al., 2014).

Again, there were differences in outcome measures and reporting. One review showed benefits restricted to the emotional domain (Schechtman & Ory, 2001) while another reported similar results for physical and mental scores (Gillison et al., 2009). Vagetti et al. (2014) used 16 sub dimensions to cover all aspect assessed by the different measures. They reported promising results, which support the efficacy of physical activity in improving HRQoL, but these findings show restricted comparability with other reviews.

Interventions, including physical activity and PRT in particular, have emerged as effective methods to improve HRQoL and are worth of further scientific pursue. However, the indistinct definition of HRQoL and variances in its assessment impede the advance of

research on this topic and highlight the need for internationally agreed standards and definitions.

1.4.3 Effects of progressive resistance training on back pain

In general, resistance exercise training proved to be eligible for the alleviation of back pain. A large network meta analysis (Owen et al., 2020) investigated the effectiveness of eleven different training interventions and identified resistance training as one of the most effective treatments, even though this evidence was reported to as low quality. This finding is supported by another meta-analysis (39 studies) on the same topic (Searle et al., 2015), ascribing strength/resistance and coordination/stabilisation exercise programs more beneficial effects than other training interventions. Posterior-chain resistance training was determined to be more effective than general exercise and walking programmes in the improvement of low back pain by a meta-analysis summarizing findings of eight trials (Tataryn et al., 2021). A review by Steele et al. (2015) assessed the significant clinical value of isolated lumbar extension resistance training and its effectiveness in the improvement of chronic low back pain. The aforementioned reviews are showing promising evidence for a general study population suffering from back pain. Surprising in this context is the limitation of literature focussed on elderly persons, particularly when considering the high prevalence of back pain among seniors (Hoy, March, et al., 2014). Despite the substantial evidence for the efficacy of PRT on musculoskeletal health in this age group, publications on its effects on disabilities originating specifically from back pain are rare. A systematic review (Ishak et al., 2016) only included the three following studies, whereas one of them did not use additional resistances for the training intervention (Hicks et al., 2013).

Hicks et al. (2013) focused on elderly individuals and investigated the influence of a mixed training intervention on LBP in 392 subjects. The 60 minutes training sessions were conducted twice a week for the duration of 12 months and included walking for warm-up (5 – 10 minutes), strengthening exercises (20 - 30 repetitions) without additional resistance (focusing on abdominal strengthening and thoracolumbar & scapula retraction) and stretching (calves and hamstrings). Participants showed improvements in back pain and functional performance. An American research group conducted two trials simultaneously (Vincent, George, et al., 2014a; Vincent, Vincent, et al., 2014b) on the same sample of 49 older obese subjects (60 – 85 years) with chronic LBP. The participants were randomly allocated to three different groups. The two intervention groups conducted whole body resistance training and a lumbar extensor training respectively (both machine-guided). The control group did not receive any form of physical

activity. One of their studies focused on the effects on walking performance (Vincent, Vincent, et al., 2014b), which is associated with back pain, the other one investigated perceived disability and pain caused by CLBP. In both cases the intervention cohorts did achieve significantly better results in four months. Walking performance was effected by both interventions in the same degree. Regarding self reported disability and pain, the whole body resistance training, which progressed continuously, achieved better results than the lumbar extensor exercises.

Another trial, not analysed in the meta-analysis of Ishak et al. (2016), included 98 older women suffering from back pain and low bone density and observed a reduction of back pain in response to a PRT intervention (Liu-Ambrose et al., 2005).

The identification of sarcopenia and muscle degeneration as risk factors for LBP (Kim et al., 2020), in tandem with the previously observed positive effects of PRT on sarcopenia (Beckwée et al., 2019; Fragala et al., 2019; Hollings et al., 2017; Hong & Kim, 2018), imply the potential beneficial influence on disability inflicted by LBP among seniors. The absence of relevant literature highlights the need for further research focussed on older subjects.

1.5 Vitamin D

The physiological effects of vitamin D and their implications for mental and physical health are a dynamic field of research. This chapter provides a small insight on the steps leading up to the current state of literature.

Vitamin D was discovered during the search for a way to cure rickets, which had become a widespread disease in the UK at the end of the 19th century. When Sir Edward Mellanby was able to treat rickets successfully through the administration of cod-liver oil, its efficacy was first related to vitamin A (Mellanby, 1919). Short after, McCollum (McCollum et al., 1922) showed that the supplementation with cod-liver oil still cured rickets after destroying the vitamin A with heat. The healing potential was then ascribed to a yet unknown essential nutrient, which was named “vitamin D”. Another cure for rickets was discovered around the same time, yet without the understanding of the mechanisms behind this effect: exposure to summer sunlight or artificial UV-radiation (Huldschinsky, 1919). Ergocalciferol (Vitamin D_2) can only be obtained from dietary sources and was the first isolated type of vitamin D (Askew et al., 1930). Some years later, cholecalciferol (vitamin D_3) was identified as the natural form of vitamin D produced in the skin from 7-dehydrocholesterol (7-DHC) in response to UVB radiation (Windaus et al., 1936). Vitamin D was disproven being a true vitamin, but kept its name.

Separate from curing rickets, another effect of vitamin D was observed early on: the supplementation of vitamin D increased serum calcium and phosphorus levels (Shipley et

al., 1925). The physiological mechanisms of this effect were identified years later: vitamin D stimulates the release of skeletal calcium into the bloodstream in response to insufficient serum calcium levels (Carlsson, 1952). This process favours bone-mineralization and neuromuscular activity, despite mobilising calcium from the bones. Serum phosphorus levels are increased by vitamin D because it facilitates the transportation of phosphate from the intestine (Chen et al., 1974).

The effects on serum calcium levels were observed with a 16-hour delay after the intake of vitamin D_3, indicating a precursory reaction (DeLuca, 1974). The identification of 25-hydroxyvitamin D_3 or calcifediol ($25(OH)D_3$) based on these observations. $25(OH)D_3$ was temporarily considered as the active form of vitamin D after its supplementation created a faster response in serum calcium levels (Blunt et al., 1968).

Yet another metabolite was isolated during further research, showing an even higher effect on serum calcium concentrations: 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$). $1,25(OH)_2D_3$ was identified as the true active metabolite of vitamin D_3 (Holick et al., 1971). Short after followed the identification of the vitamin D_2 metabolites, 25-hydroxyvitamin D_2 ($25(OH)\ D_2$) and 1,25-dihydroxyvitamin D_2 ($1,25(OH)_2D_2$) (Jones et al., 1975).

The liver (Ponchon et al., 1969) and the kidneys (Brunette et al., 1978) were identified as the primal sites of the vitamin D metabolism. The hepatic transformation from vitamin D to 25(OH)D proceeds the renal creation of $1,25\text{-}(OH)_2D_3$ from 25(OH)D. $1,25\text{-}(OH)_2D_3$ is then transported to the vitamin D target tissues. Subsequent research ascribed tentative paracrine and/or autocrine functions to $1,25\text{-}(OH)_2D_3$ after observing its extrahepatic formation (DeLuca, 2014).

Since vitamin D was first identified with bone health, research was focussed on skeletal disorders. Its vital role in bone health is well-documented with various publications (Bikle, 2012; Christakos et al., 2020; Cranney et al., 2007; Laird et al., 2010)

In recent years, the scientific interest on vitamin D has been growing continuously and research extended from skeletal to non-skeletal health outcomes. Among others, studies observed influences on cancer (Grant, 2018), multiple sclerosis (Mokry et al., 2015), cardiovascular diseases (Lavie et al., 2011), diabetes (Mathieu, 2015), inflammation levels (Mousa et al., 2018), obesity (Ardawi et al., 2011), immune function (Prietl et al., 2013) and respiratory tract infections (Bergman et al., 2013).

Serum 25(OH)D concentrations are also related to mental health (Gugger et al., 2019), depression (Jaddou et al., 2012), general well-being (Oh et al., 2017) and increasingly with HRQoL (Ecemis & Atmaca, 2013; Kim et al., 2015; Oh et al., 2017; Palazzo et al., 2019).

With the on-going pandemic at hand, researchers try to relate serum vitamin D status to Covid-19 and to detect mechanisms responsible for suggested influences (Kalia et al.,

2020; Shojaeefar et al., 2021). Studies identified low vitamin D levels as a risk factor for Covid-19 and is associated with the severity of its course (Demir et al., 2021; Merzon et al., 2020). There is also tentative evidence, that vitamin D supplementation is effective in the treatment and the prevention of Covid-19 (Teymoori-rad & Marashi, 2020).

The reported associations of vitamin D with a broad range of physical and psychological health conditions indicate its manifold effects within the human body and complex physiological mechanisms.

A short summary of vitamin D terminology is provided in table 1.

Table 1: Vitamin D nomenclature

Name (Abbreviation)	Frequent synonyms	Description
7-dehydrocholesterol (7-DHC)	-	Sterin converted into previtamin D_3 upon exposure to UVB radiation in the skin
Previtamin D_3	-	Intermediate in the formation of vitamin D_3 from 7-DHC
Vitamin D_3	Cholecalciferol, Calciol	Inactive form of dietary (animal-based) and natural vitamin D_3 before hepatic hydroxylation
Vitamin D_2	Ergocalciferol, Calciferol	Inactive form of dietary (plant-based) vitamin D_2 before hepatic hydroxylation
25-hydroxyvitamin D_3 (25(OH) D3)	Calcifediol, Calcidiol, 25-hydroxycholecalciferol	Inactive hormonal form of vitamin D_3 after hepatic hydroxylation (prehormone)
1,25-dihydroxyvitamin D_3, ($1,25(OH)_2D_3$)	Calcitriol, decostriol, 1,25-dihydroxycholechalciferol	Active hormonal form of vitamin D_3 after renal hydroxylation (hormone)
Calcitroic acid	-	Excretory product of the reduction of $1,25(OH)_2D$

The use of “D” only, when referring to vitamin D metabolites, describes both types D_2 and D_3 collectively.

1.5.1 Vitamin D metabolism and production

Vitamin D is either provided through dietary intake or synthesized naturally in the skin (Girgis et al., 2013). A short summary of the processes involved in the production of the vitamin D metabolites was provided in the last chapter. The following pages will address in more detail the physiological mechanisms behind the effects of vitamin D.

Upon exposure to UVB radiation (wavelengths between 290 and 315 nm) 7-DHC, a sterin present in the epidermis, is transformed to the semi-steroid pre-vitamin D_3 (Holick, 2007). This compound is subsequently converted to vitamin D_3 through thermal isomerization (heat). Vitamin D_3 is then released into the epidermal extracellular space from where it diffuses into the capillary network of the dermis. After attaching to the vitamin D binding protein (DBP), vitamin D_3 is transported either to the liver for further metabolism (Wacker & Holick, 2013b) or to the fat tissue for storage (Martinaityte et al., 2017). DBP is

responsible for the transportation of vitamin D and its metabolites to their respective sites of metabolism and target tissues (Norman, 2008).

While the bodily photochemical creation only results in vitamin D_3, vitamin D obtained from nutrition is either plant-based vitamin D_2 or animal-based vitamin D_3. Both types are fat-soluble and get absorbed in the small intestine. With the help of lipoproteins (chylomicrons) vitamin D is then transported into the lymph vessels and further into the bloodstream (Kohlmeier, 2003). Vitamin D is partially absorbed by adipose tissue (storage) before arriving at the liver, where it enters the same pathway as naturally produced vitamin D (Quesada-Gomez & Bouillon, 2018).

In order to execute its functions further metabolism of vitamin D is necessary, consisting of three main stages: 25-hydroxylation, 1α-hydroxylation, and 24-hydroxylation. These steps are performed by respective enzymes of the same type, the cytochrome P450 mixed-function oxidases (CYPs) (Bikle, 2014).

The 25-hydroxylation of vitamin D to the pro-hormone 25(OH)D takes place in the liver. There are various CYPs capable of 25-hydroxylation, including CYP27A1 and CYP2R1 (Bikle, 2014). CYP2R1 is mainly expressed in the liver and is estimated as the most important enzyme for the creation of 25(OH)D in humans (Girgis et al., 2013). It is able to convert both, vitamin D_2 and D_3, while CYP27A1 only uses vitamin D_3 as a substrate (Bikle, 2014). Despite the presence of CYP2R1 and CYP27A1 in other tissues (kidneys, testes), the liver is the main, or even the exclusive site of vitamin D 25-hydroxilation.

25-hydroxilation is a saturated process and excessive amounts of vitamin D, the precursor of 25(OH)D, are stored in the body fat and slowly released on demand (Mazahery & Von Hurst, 2015). The storage of 25(OH)D itself was observed in skeletal muscle tissue, from where it re-enters the blood circulation (Rybchyn et al., 2020). The hepatic formation of 25(OH)D is only loosely regulated (Bikle, 2014). 25(OH)D shows higher plasma concentrations and a longer half-life (approximately 21 days) compared to other vitamin D metabolites (Helde-Frankling & Björkhem-Bergman, 2017). These characteristics established circulating 25(OH)D levels as the most common and reliable maker for overall vitamin D status.

The next step in the vitamin D metabolism is the conversion of the still physiologically inactive 25(OH)D to the active hormonal 1,25-$(OH)_2$D through 1α-hydroxylation (Bikle, 2014). CYP27B1 is the sole enzyme responsible for this transformation, which mainly takes place in the renal proximal tubule (DeLuca, 2014). The expression and activity of CYP27B1 is not restricted to the kidneys only, but also observed in numerous other tissues (i.e. skin, lungs, breast, intestine, endocrine glands, thyroid, osteoblasts and chondrocytes). The presence of CYP27B1 throughout the human body indicate paracrine and autocrine functions of 1,25-$(OH)_2$D (Bikle, 2014).

From the kidneys, the active metabolite is transported to its target tissues including the bone, brain, lung and muscle (Norman, 2008). After transportation to its target tissues it binds to the local vitamin D receptors (VDR) in order to employ its physiological functions (Pludowski et al., 2018).

Main regulatory factors of CYP27B1 are the parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23), serum calcium/phosphorus levels and 1,25-$(OH)_2$D itself (Panda et al., 2004). PTH up-regulates the renal synthesis of 1,25-$(OH)_2$D, while FGF23 shows a down-regulating effect. Low calcium levels cause rising PTH levels and high phosphorus concentrations create augmented FGF23 levels, regulating the creation indirectly. (Jones et al., 2012) 1,25-$(OH)_2$D down-regulates itself through three different mechanisms: Firstly through the inhibition of CYP27B1 expression (Henry, 2011), secondly by causing reduced PTH secretion (Norman, 2008) and lastly by inducing 24-hydroxylase, which is the degradation process of 1,25-$(OH)_2$D (Jones et al., 2012). 1,25-$(OH)_2$D is reduced to its biologically inactive residue calcitroic acid by CYP24A1 only, generally through 24-hydroxilation (Girgis et al., 2013). This breakdown happens in a series of reactions and creates various intermediate metabolites along the pathway (DeLuca, 2014). Some of these intermediates are still physiologically active, such as 1,24,25$(OH)_3$D which shows affinity for VDR (Bikle, 2014).

25(OH)D can also be substrate for 24-hydroxilation and is degraded in a similar fashion as 1,25-$(OH)_2$D (St-Arnaud & Jones, 2018). CYP24A1 can also induce the breakdown of 1,25-$(OH)_2$D and 25(OH)D through 23-hydroxylization, which again results in the residue calcitroic acid (Jones et al., 2012)

The main activity of CYP24A1 is preventing extensive serum 1,25-$(OH)_2$D and 25(OH)D levels and is restricted to the kidneys only. However, CYP24A1 is present in all tissues containing VDR where it is assumed to fine-adjust 1,25-$(OH)_2$D concentrations, in order to ensure proper response functions (Jones et al., 2012).

The reduction of 1,25-$(OH)_2$D is regulated by the same factors as its creation, but the effects are reciprocal, at least in the kidneys. In other tissues, CYP24A1 shows varying regulatory effects suggesting cell specific regulation of the 24-hydroxylase (Bikle, 2014).

These complex mechanisms illustrate the sensitivity of the vitamin D metabolism. Looking at the information in this chapter, the pathway of vitamin D can be impaired in different ways. Disorders of the gastrointestinal tract (absorption) (Leslie & Hankey, 2015), the liver (25-hydroxylation) (Nair, 2010) or the kidneys (1α-hydroxylation, 24-hydroxilation) (Franca Gois et al., 2018) can influence vitamin D production in a negative way. Irregularities on a enzymatic (Malloy & Feldman, 2010) (VBP, VDR, CYPs) and hormonal (Demer et al., 2018)(1,25-$(OH)_2$D, PTH, FGF23) level can also create unfavourable effects on the vitamin D metabolism. The vitamin D metabolism is displayed in figure 1.

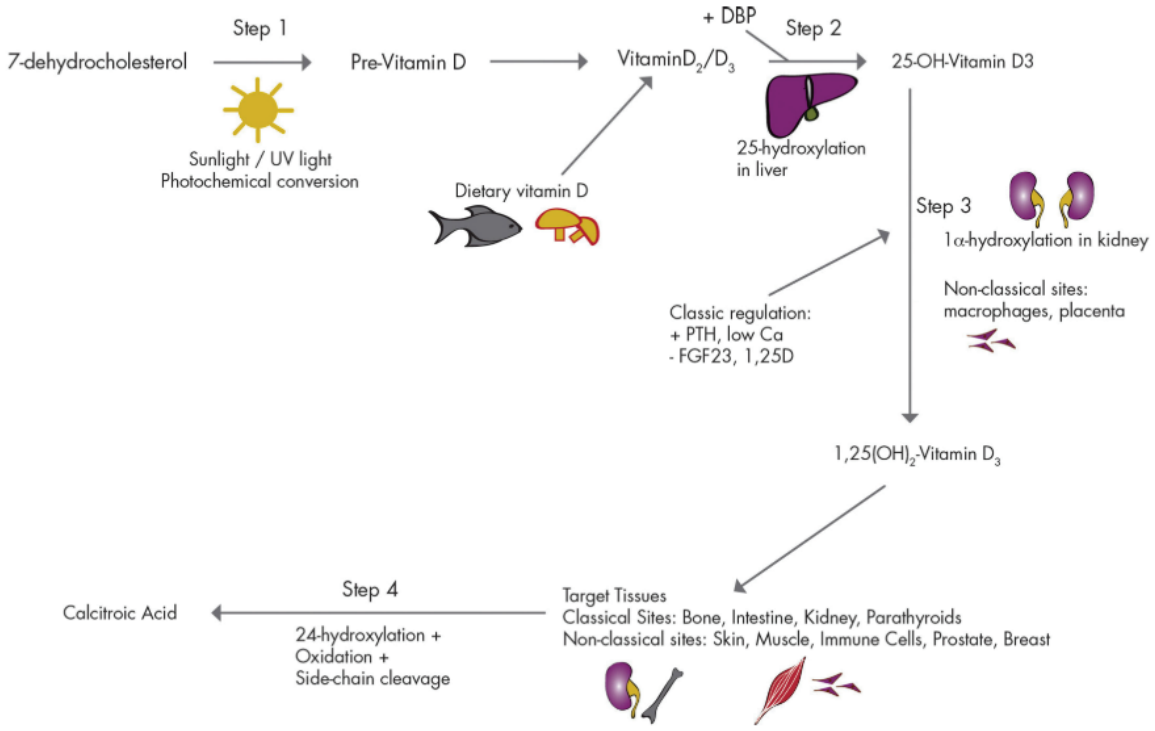

Figure 1: Illustration of the vitamin D metabolism (Girgis et al., 2013).

There are also factors affecting the natural production of vitamin D_3 and subsequently have an impact on the natural vitamin D_3 supply.

1.5.2 Factors influencing the natural vitamin D_3 production

Several parameters take influence on the photochemical conversion of 7-DHC to previtamin D_3 in the skin. These factors can be roughly divided into external, personal and behavioural factors.

External factors include latitude, season, altitude and time of day. These parameters influence the amount of UVB radiation reaching a point on the earth's surface at a certain time. Different radiation levels are caused by changes in the solar zenith angle (SZA) (Schrempf et al., 2017) and the seasonal variety of earth's distance from the sun (Kimlin, 2008). The SZA can be defined as the "angle between the local vertical (zenith) and the position of the sun at any given moment" (Kimlin, 2008). The vast majority (99%) of UVB radiation is absorbed by the stratospheric ozone layer, even at lowest SZA in summer at noon, (Wacker & Holick, 2013b). The absorption rate increases with growing SZA, since the photons have to travel further (Wacker & Holick, 2013a) and due to extended scattering of the sun's light (Kimlin, 2008). Consequently, the production of vitamin D_3 via photosynthesis is hardly possible during winter months (November to March) when living at latitudes above or below 33° (Wacker & Holick, 2013b). Augmented levels of air

pollution and cloud coverage also decrease the amount of UVB radiation reaching the earth's surface (Kimlin, 2008).

Personal parameters, such as age and skin pigmentation, determine an individual's capacity for cutaneous vitamin D_3 production. The melanin in the human skin absorbs UVB radiation and raised skin pigmentation mitigates the amount of UVB radiation reaching the epidermis for vitamin D_3 production. 7-DHC concentrations in the skin are declining with age, leading to a decrease in efficiency of natural vitamin D_3 synthesis throughout the lifespan (Wacker & Holick, 2013a). Aging also shows detrimental effects on VBP expression, which impedes the bodily transportation of the vitamin D_3 metabolites (Mazahery & Von Hurst, 2015).

Behavioural factors also influence the amount of vitamin D_3 obtained through photoconversion. Clothing and staying in the shadow/inside prevent the natural production of 7-DHC. The use of sun screen with UVB filter reduces the efficiency of vitamin D_3 photoconversion by at least 97,5% (Holick, 2017). Vitamin D_3 intoxication is not possible in response to bodily synthesis, since the sun destroys excessive pre-vitamin D_3 and vitamin D_3 directly in the skin (Wacker & Holick, 2013b).

Most people are not able to cover their vitamin D supply with natural production. The share of vitamin D deficient persons in Europe is estimated to be 40%. The prevalence of vitamin D deficiency in Europe is dependent on latitude and season, with lower average serum 25(OH)D concentrations in winter and the among the population of the northern hemispheres (Amrein et al., 2020). The supplementation of vitamin D appears inevitable in order to maintain an adequate vitamin D status throughout the year.

1.5.3 Vitamin D supplementation

Vitamin D contents of foods or supplements are generally provided in µg or in international units (IU) with 1 µg equalling 40 IU (European Food Safety Authority, 2014).

Only few aliments contain vitamin D and contents differ between foods. The highest concentrations are generally found in eel (1200 IU/100g) and cod liver oil (400 – 1000 IU/tsp). Cutaneous photoconversion approximately produces between 2000 and 4000 IU with arms and legs exposed to 0.5 minimal erythemal dose (MED) of UVB radiation. (Pludowski, Holick, et al., 2013). The time exposed to UVB radiation, which is needed to produce a certain amount of vitamin D, is hard to define, since it is dependent on several factors, described in the last chapter.

Foods containing vitamin D are rare (Webb et al., 2018) and the time spent outside is decreasing in the population. Vitamin D supplementation is an effective method to ensure an adequate vitamin D status throughout the year, especially when living in latitudes below/above 33°, as in Austria (Wacker & Holick, 2013a).

1.5.3.1 Vitamin D level measurement

Initially, the validity of the two vitamin D metabolites 25(OH)D and 1,25-$(OH)_2$D of vitamin D to represent overall vitamin D status was unclear.

It was observed, that 1,25-$(OH)_2$D remains in the blood serum for a short period of time and its renal creation is tightly regulated. It is only produced on demand and shows very low concentrations after adequate vitamin D levels are reached (DeLuca, 2014). Contrary to the production of 1,25-$(OH)_2$D, the creation of 25(OH)D is barely regulated. The inactive metabolite additionally provides information on vitamin D reserves, since it remains present in the serum even if not immediately required (Bikle, 2014). Consequently, 25(OH)D was established as the most reliable clinical marker of vitamin D levels, assessing supply from diet and photoconversion (Bahrami et al., 2018). Serum 25(OH)D concentration are generally stated in ng/ml or nmol/l (1 ng/ml = 2.496 nmol/l) (European Food Safety Authority, 2014).

1.5.3.2 Optimal vitamin D levels

The expert opinions on the topic of recommended vitamin D levels differ (Pludowski et al., 2018). A commonly used threshold for vitamin D sufficiency in research was suggested by the Endocrine Society and is set at a serum 25(OH)D concentration of 30 ng/ml (Holick et al., 2011). This concentration is based on the Recommended Dietary Allowance (RDA), which assures adequate amounts of vitamin D for 97,5% of the population (Cashman, 2018). The guidelines of the Endocrine Society also include concentration levels defining vitamin D insufficiency (20 - 29 ng/ml) and deficiency (< 20 ng/ml) (Holick et al., 2011). These definitions are in line with guidelines directed at the Central European population (Pludowski, Karczmarewicz, et al., 2013).

Critics state, that the use of the RDA for this purpose create deceivingly high prevalence ratios of vitamin D insufficiency and deficiency and lead to numerous cases of unnecessary supplementation (Taylor et al., 2017). Other guidelines do not differentiate between insufficiency and deficiency and set the optimal vitamin D status as serum 25(OH)D concentrations above 20 ng/ml (European Food Safety Authority, 2014; German Nutrition Society, 2012; Ross et al., 2011).

Thresholds and RDA are based on concentrations, which either proved to successfully prevent vitamin D related health outcomes, or create plateauing PTH levels as an indicator of down-regulation (Holick et al., 2011). Diseases are effectively prevented at different minimum serum 25(OH)D concentrations. Relatively low vitamin D levels are needed to effectively avert skeletal disorders like rickets (10 ng/ml), osteoporosis or fractures (both 20 ng/ml). Higher requirements are reported for the preventions of non-

skeletal diseases, such as depression (30 ng/ml), cardiovascular disorders (32 ng/ml), falls (38 ng/ml) and cancer (40 ng/ml) (Spedding et al., 2013).
The thresholds provided in guidelines can be seen as valid and sophisticated indications for favourable serum 25(OH)D concentrations, but they might not meet the requirements of certain individuals or the prevention of a distinctive disease.

1.5.3.3 Factors affecting vitamin D supplementation

There are several factors influencing the increase of 25(OH)D concentrations in response to vitamin D supplementation. Lower basal 25(OH)D concentrations are associated with higher improvements in vitamin D status, since the process of hepatic 24-hydroxilation might get saturated earlier with higher basal vitamin D levels (Mazahery & Von Hurst, 2015).
Body mass index (BMI) or rather body fat mass correlates negatively with the rise of 25(OH)D concentrations in response to supplementation. Vitamin D is stored in the body fat and only released over time, causing a delay in the rise of serum 25(OH)D levels (Martinaityte et al., 2017).
The administration of vitamin D alongside poly-unsaturated fatty acids alleviate the intestinal absorption of the liposoluble supplement and create greater gains in serum 25(OH)D concentration. Gastrointestinal diseases impede the absorption rates of vitamin D and certain types of medication (antiepileptic drugs, glucocorticoids, lipase inhibitors) showed detrimental effects on 25(OH)D concentrations (Mazahery & Von Hurst, 2015).
The preferred compound used for supplementation is vitamin D_3. Its administration showed significantly higher increases of serum 25(OH)D concentration and better results in maintaining good vitamin D status, when compared to the use of vitamin D_2 (Heaney et al., 2011). There is increasing consensus against the use of vitamin D_2 for supplementation (Autier et al., 2012; Heaney et al., 2011; Houghton & Vieth, 2006; Mazahery & Von Hurst, 2015). Vitamin D_3 was reported to be 87% more potent in rising serum 25(OH)D levels and it was ascribed a two to three fold greater vitamin D storage capacity (Heaney et al., 2013). Vitamin D_2 shows a lower affinity to VBP and has a shorter half-life than vitamin D_3 (Bikle, 2014). Although vitamin D_2 has been proven to increase 25(OH)D levels, there is evidence, that it might also cause a decrease of serum 25(OH)D concentrations, because it might impede the metabolism of vitamin D_3 (Mazahery & Von Hurst, 2015).
Another form of vitamin D used for supplementation is 25(OH)D_3, but opinions on its administration are diverging. It holds some apparent advantages over vitamin D_3, such as its higher potency (two to threefold) to increase serum 25(OH)D levels. It also shows better intestinal absorption rates and shorter response time of serum 25(OH)D

concentrations after administration. Furthermore its efficacy is not related to the basal vitamin D status (Quesada-Gomez & Bouillon, 2018). Critics of $25(OH)D_3$ supplements claim, that it has no real clinical advantages, when the dose of vitamin D_3 is adequately increased to match the potency of $25(OH)D_3$. Further the administration of $25(OH)D_3$ seems artificial, since vitamin D_3 is the type also naturally produced in the skin (Vieth, 2020).

$1,25(OH)_2D_3$ can also be used for vitamin D supplementation, but requires attentive monitoring. It is generally only used as hormone replacement in subjects showing severely impeded renal 1α-hydroxylation (Vieth, 2020). Apart from the type of vitamin D, supplementation strategies can differ in dose, duration and frequency of vitamin D administration.

Generally higher doses are associated with greater overall increase of 25(OH)D concentrations. If supplements are taken in form of high concentrated boluses the response of vitamin D levels might show a flatter curve than the same amount administered in smaller and more frequent doses. The saturation of hepatic 25-hydroxilation changes the reaction from one to zero order, which means the rate of 25-hydroxilation becomes independent from the concentration of its precursor vitamin D (Mazahery & Von Hurst, 2015). A high bolus leads to the storage of the excessive vitamin D in fat tissue, which is then steadily released for 25-hydroxilation. The impact of stored vitamin D was even reported one year after a prolonged supplementation (Martinaityte et al., 2017). A higher compliance rate can be assured with intermittent administration of vitamin D, compared to a daily regime (Mazahery & Von Hurst, 2015) The exact influence of overall duration is unclear and seems negligible, since variations of serum 25(OH)D concentrations in response to supplementation are mainly dose-dependent (Mazahery & Von Hurst, 2015).

1.5.3.4 Reference Dietary Intake and Tolerable Upper Intake

The aforementioned guidelines also suggest the Reference Dietary Intake (RDI), which is the daily vitamin D supply (diet and photoconversion) needed to achieve the respective target serum 25(OH)D concentrations. RDIs range from 400 to 600 IU/day for neonates and infants (< 1 year) and from 600 to 2000 IU/day for all older subjects. Some of the guidelines offer distinctive RDIs for younger and older adults, which recommend higher dosages with increasing age (Holick et al., 2011; Pludowski, Karczmarewicz, et al., 2013; Ross et al., 2011). The lowest RDI recommended for elderly subjects is 600 IU/day (European Food Safety Authority, 2014) and the highest is 1500 – 2000 IU/day (Holick et al., 2011). Obese individuals with a BMI over 30 kg/m^2 should take at least the two- to three-fold amount of vitamin D per day compared to subjects with normal weight. 1500 to

2000 IU/day is reported as RDI for pregnant or breastfeeding women (Holick et al., 2011; Pludowski, Karczmarewicz, et al., 2013).

Tolerable Upper Intake Levels (ULs) are the highest average daily intakes of vitamin D that are unlikely to create adverse effects. They are reported to be 1000 IU/day for infants (<1 year) and 2000 IU/day for children (1-10 years). ULs for older subjects (> 10 years) are 4000 IU/day for those with normal weight and 10000 IU/day for obese individuals (Holick et al., 2011). Holick et al. (2011) also recommend to treat adults suffering from vitamin D deficiency with 50000 IU of vitamin D once a week (or 6000 IU/day) for the duration of two months, in order to push serum 25(OH)D concentrations above 30 ng/ml. The subsequent dosage should be between 1500 and 2000 IU/day to assure the maintenance of adequate vitamin D levels. RDIs, ULs and definitions of vitamin D sufficiency, insufficiency and deficiency are summarized in table 2.

Table 2: Vitamin D RDIs, ULs and recommended status

Age [years]		IOM	EFSA	DACH	Cent. Euro.	End. Soc.
0 – 0.5	RDI [IU]	400	400	400	400	400 - 1000
	UL [IU]	1000	1000	1000	1000	1000
0.5 – 1	RDI [IU]	400	600	800	600 - 1000	400 - 1000
	UL [IU]	1500	1000	1000	1000	1500
1 – 18	RDI [IU]	600	800	800	600 - 1000	600 - 1000
	UL [IU]	2500 - 4000	2000 - 4000	-	2000 - 4000	2500 - 4000
19 - 70	RDI [IU]	600	800	800	800 - 2000	1500 - 2000
	UL [IU]	4000	4000	-	4000	4000
>70	RDI [IU]	800	800	800	800 - 2000	1500 - 2000
	UL [IU]	4000	4000	-	4000	4000
Sufficiency		-	-	-	> 30 ng/ml	> 30 ng/ml
Insufficiency		-	-	-	20 - 30 ng/ml	20 - 30 ng/ml
Deficiency		-	-	-	< 20 ng /ml	< 20 ng /ml
RDA*/optimal		20 ng/ml*	20 ng/ml	20 ng/ml		
1 µg = 40 IU **1 ng/ml = 2.496 nmol/l**		(Ross et al., 2011)	(European Food Safety Authority, 2014)	(German Nutrition Society, 2012)	(Pludowski, Karczmarewicz, et al., 2013)	(Holick et al., 2011)

IOM (Institute of Medicine); EFSA (European Food Safety Authority); DACH (Germany, Austria, Switzerland); Cent. Euro. (Central Europe), End. Soc. (Endocrine Society); RDI (Reference Dietary Intake); UL (Tolerable Upper Intake Level), RDA (Recommended Daily Allowance); IU (internationtal unit); ng/ml (nanogram per millilitre); µg (microgram); nmol/l (nanomol per litre)

Vitamin D intoxication is quite unlikely and rarely reported in literature, since excessive vitamin D from the photoconversion of 7-DHC is already destroyed in the skin before it

enters the metabolic pathway and tolerable upper intakes are quite high. Signs of intoxication only occur after prolonged intake of highly immoderate doses of vitamin D, which has to create persistent serum 25(OH)D concentrations over 200 ng/ml (Holick, 2017). Typical early symptoms are hypercalcemia and hyperphosphatemia caused by enhanced calcium and phosphorus mobilization (Danielewicz, 2013). If left untreated vitamin D intoxication can cause kidney failure, calcification of soft tissue (i.e. blood vessels & kidneys) and eventually death (Wacker & Holick, 2013a).

1.5.4 Effects of vitamin D on quality of life

HRQoL has been associated with serum 25(OH)D concentrations worldwide in younger (Ecemis & Atmaca, 2013; Oh et al., 2017; Palazzo et al., 2019) and older populations (Chao et al., 2014; H. J. Kim et al., 2015) alike. All of these studies reported significantly lower physical and mental HRQoL in subjects, which suffered from vitamin D deficiency or insufficiency than in individuals with higher vitamin D levels. These findings propose that higher vitamin D status might lead to better HRQoL.

Looking into previous intervention trials among elderly persons, there is substantial prove of the beneficial effects of vitamin D supplementation on the mental and physical dimensions of HRQoL in healthy (Gao et al., 2015; Motsingera et al., 2012; Ramly et al., 2014) and diseased subjects (Abbasnezhad et al., 2016; Costan et al., 2014; Dogru et al., 2017; Gugger et al., 2019; Sanders et al., 2011; Yilmaz et al., 2016). However, other studies did not report any significant effects of vitamin D administration on HRQoL in older populations (Grimnes et al., 2017; Grove-Laugesen et al., 2020; Prins & Heijer, 2017; Witham, Crighton, et al., 2010).

At a closer look, participants in two of these studies showed baseline serum 25(OH)D concentrations already near to vitamin D sufficiency, what might explain the missing additional effects of supplementation on HRQoL (Grimnes et al., 2017; Grove-Laugesen et al., 2020). Another trial (Witham, Crighton, et al., 2010) used vitamin D2, which was proven less effective to improve vitamin D status than other supplements (Houghton & Vieth, 2006) and the subjects were on average still vitamin D deficient post-intervention. The subjects allocated to the vitamin D supplementation group in the study of Prins and Heijer (2017) showed high average baseline BMI values, very close to obesity. Although the daily supplementation dose of 1200 IU was far below the respective recommendations for obese individuals of 4500 to 6000 IU/day (Holick et al., 2011), the average serum 25(OH)D concentration were increased above the sufficiency threshold after 6 months. However, the study only included 50 subjects and they all suffered from COPD. The small sample size and potential effects of their disorder might have impeded the improvement in HRQoL in response to the vitamin D supplementation.

Literature on this topic is still scarce and the determination of valid conclusions imposes certain challenges. A systematic review by Hoffmann et al. (2015) included 15 studies on this topic and resulted in the mere indication of a small to moderate effect of short-term vitamin D supplementation on HRQoL in diseased individuals. Implications for other subjects or durations were inconclusive, due to methodological inconsistencies and wide differences in outcome measures and study populations. The review was not able to provide recommendations of favourable supplementation regimes, since the intervention protocols varied broadly in type, dose and frequency of vitamin D administration. These limitations also prevented the authors from the conduction of a meta-analysis, as initially intended.

A standardized quantification and definition of HRQoL is still missing and questionnaires show limited comparability, even though they might assess similar sub-domains. The use of generic measures alleviates the comparison of results. To draw conclusions for the conduction of future trials the efficacy of previously used supplementation protocols has to be interpreted carefully, with a close look on possible factors influencing the serum 25(OH)D concentration response.

1.5.5 Effects of vitamin D on back pain

The literature on the effects of vitamin D supplementation on back pain in older adults is limited and the following findings are retrieved from studies with younger populations. A systematic review (n = 29) and meta-analysis (n = 22) of observational studies (Zadro et al., 2017) generally associated LBP with vitamin D deficiency, especially in younger females and severely deficient subjects. The same authors published a systematic review (n = 8) and meta-analysis (n = 6) on the effects of vitamin D supplementation on LBP (Zadro et al., 2018). Despite the previously proven relation between serum 25(OH)D concentration and back pain, they were not able to identify any additional benefits of vitamin D supplementation compared to other interventions (pharmacological, placebo) or no intervention at all. However, these findings seem inconclusive, since the review did only include a small number of trials that showed poor methodological quality and low sample sizes.

Looking into further trials on the topic, there is evidence for the effectiveness of vitamin D supplementation to alleviate back pain. The 16-week RCT of Brady et al. (2019) included overweight and obese adults suffering from vitamin D deficiency and reported high increases of serum 25(OH)D concentrations in response to the supplementation regime. They were able to attribute the significant improvements in self-reported back pain disability to the vitamin D_3 intervention.

A large quasi-experimental trial (Akhtar et al., 2020) was conducted with 600 adults

suffering from chronic LBP. The vitamin D_3 supplementation increased the serum 25(OH)D concentrations and created beneficial effects on perceived back pain (VAS) and functional disability (modified Oswestry disability questionnaire) in addition to standard therapy. These findings are in line with a single arm open-label study including 68 individuals reporting CLBP (Ghai et al., 2017). Perceived pain (VAS) and functional disability (modified Oswestry disability questionnaire) were assessed before and two, three and six months after vitamin D_3 supplementation. Both scores had been positively influenced by vitamin D3 supplementation. Dzik et al. (2018) investigated the impact of vitamin D_3 on LBP from another perspective, by retrieving paraspinal skeletal muscle samples from 38 LBP patients and quantifying markers of oxidative stress. The markers were significantly reduced after five weeks of vitamin D_3 supplementation.

These findings provide evidence for the alleviation of perceived pain and functional disability related to LBP in response to vitamin D supplementation. The high prevalence of disability caused by LBP among the elderly (Hoy, March, et al., 2014) in tandem with limited literature focussed on older persons highlight the need for further research in this context.

1.6 Overview of combined vitamin D and training interventions

Due to the physical, mental, nutritional, social and emotional changes related to aging, older persons are exposed to a higher risk of impaired HRQoL (Klompstra et al., 2019). The conduction of a combined PRT and vitamin D supplementation intervention seems eligible to aim for improvements in HRQoL in an elderly population. PRT (Cheema et al., 2014; Hart & Buck, 2019) and vitamin D supplements (Yilmaz et al., 2016) were independently proven effective to increase all dimensions of HRQoL. Decline in muscle function are commonly observed factors causing decreased HRQoL in older subjects (C Beaudart et al., 2017; Sun et al., 2019). There is substantial evidence for the efficacy of PRT to create positive changes in muscle function in older individuals (Latham et al., 2004; Liu & Latham, 2011; Papa et al., 2017). Vitamin D supplementation was also able to improve muscle function in vitamin D deficient elderly populations (Charlotte Beaudart et al., 2014; Stockton et al., 2011). Further, older persons represent the least active age group (Chodzko-Zajko et al., 2009) and risk of vitamin D deficiency is increasing along age due to the decreased capacity of natural vitamin D_3 synthesis(Meehan & Penckofer, 2014).

The literature on the topic is yet scarce and shows strong methodological variances. Nevertheless a short review of 6 trials (Abizanda et al., 2015; Berens et al., 2018; Ekwaru et al., 2016; Matthews et al., 2020; Patil et al., 2016; Renerts et al., 2019) might shed some light on previously reported outcomes, even if most of them did not use PRT, but

other types of exercise. Four of these trials did report beneficial intervention effects on the quality of life (Abizanda et al., 2015; Ekwaru et al., 2016; Matthews et al., 2020; Renerts et al., 2019), while one was not able to identify any influences (Berens et al., 2018; Patil et al., 2016).

Looking first into the RCTs without reported improvements, one of them (Patil et al., 2016) showed relatively high mean baseline vitamin D levels (> 26 ng/ml) for the whole study sample, consisting of community-dwelling Finish older women. The high basal serum 25(OH)D concentrations might have impaired the improvements in response to supplementation, considering the assumed threshold at which additional vitamin D administration does not provide any extra benefit (Mazahery & Von Hurst, 2015). As for the null-findings regarding the exercise intervention the authors could not exclude the possibility, that the subjects had already been engaged in physical activity before, thus exceeding the average extend of the general population, what might consequently have reduced the effects of the exercise intervention. Lastly Patil et al. (2016) did question the sensitivity for changes of the outcome measures, but this seems to be a general issue in the quantification of quality. The other trial (Matthews et al., 2020) not reporting improvements in response to the combined intervention (1 year) showed baseline vitamin D levels, which were already far above the sufficiency threshold. This might explain the missing effect of vitamin D supplementation. The participants showed limitations in mobility, what might have impeded the efficacy of the training regime.

One of the RCTs (Berens et al., 2018), which reported positive effects of the intervention on the mental and emotional dimension of the SF-36, did not report an additional effect of the vitamin D supplementation. The authors attributed the improvements to the training and explained the missing nutritional influence with baseline BMI scores above average. The daily dose of 800 IU was fairly low in this context.

The 2 × 2 factorial trial (800 vs. 2000 IU vitamin D3 per day; no exercise vs. exercise) of Renerts et al. (2019) investigated intervention effects over twelve months on health-related quality of life in 173 mostly community-dwelling subjects (79% females) with a mean age of 84 years and baseline mean serum 25(OH)D concentration of 12.6 ± 8.0 ng/ml. They all recently received hip fracture surgery, and although observing a decline in quality of life for all patients over the first 6 months, a further decrease in the second phase was prevented in all three intervention groups, contrarily to the further decline in the low-dose cohort.

Ekwaru et al. (2016) analysed the data of 2119 Canadian subjects above the age of 50, who had entered in a preventive one-year program, promoting a healthy lifestyle, physical activity and vitamin D supplementation. They associated increases in serum 25(OH)D concentration with improvements in quality of life. However, no detailed information on

basal vitamin D status, supplementation dosage or type and extent of physical activity could be obtained from their reporting. The observational study of Abizanda et al. (2015) included 91 frail and institutionalised subjects (> 70 years) and analysed the effects of a standardized exercise program in combination with the administration of a multicomponent supplement, also containing 1000 IU of vitamin D_3, on physical function and quality of life. The twelve-week intervention did improve physical functioning and quality of life; better results were associated with lower basal vitamin D levels, which were not reported in the article.

All studies combined physical activity and vitamin D supplementation, but the comparability of these trials is rather low. Crucial data, such as baseline vitamin D levels, was sometimes not reported. The trials show strong diversities in study design, duration and population and assessment of HRQoL. However, looking at the provided data, longer intervention periods and lower baseline 25(OH)D concentrations created more favourable improvements in HRQoL.

The absence of uniformity in this field of research is apparent, which impedes the identification of analogies or deviations with other trials. Some of the studies showed poor methodological quality and did not provide relevant baseline values. Nevertheless, there is tentative evidence for the efficacy of combined intervention, especially in deficient subjects and with prolonged training interventions. The use of a controlled study design, thorough reporting and the use of generic HRQoL measures can be recommended for the conduction of future trials to successfully progress research on this promising topic.

1.7 Aims of this study

The share of older people is increasing all around the world (World Health Organisation, 2021) and more people will be confronted with the negative consequences of aging without efficient and simple counter measures.

Older individuals are exposed to a high risk of impaired musculoskeletal health (Larsson et al., 2019) and of disability caused by LBP (Hoy, March, et al., 2014), which are both associated with reduced HRQoL (Fatouros et al., 2005). Progressive resistance training is an established measure to reduce back pain (Owen et al., 2020; Searle et al., 2015), but shows lacking research among seniors (Ishak et al., 2016). Vitamin D supplementation is positioned as a promising, yet not fully understood tool to positively influence muscular function (Grimnes et al., 2017). Further, there is tentative evidence for the effectiveness of the combination of these two intervention measures to improve HRQoL (Renerts et al., 2019), but combined studies are still very rare, especially in the form of an randomized controlled trial.

To advance research on this emerging field of science, these two interventions were combined, also including the mental burden of age-related disability by evaluating the outcomes from a patient-centred perspective. The present study assessed the efficacy of these interventions by investigating their effects on HRQoL (physical and mental function) and perceived disability created by LBP in a population of healthy community dwelling older subjects.

These two interventions were implemented consecutively to evaluate the isolated effects of vitamin D_3 supplementation only, and subsequently in combination with PRT. The parameters of HRQoL and disability experienced from back pain were assessed with two generic self-reported questionnaires to assure comparability with other research:

the SF-36 (quality of life) and the Roland-Morris Disability Questionnaire (RMDQ) (back pain).

There are differences in the recommended vitamin D RDIs in literature. Therefore, a high- and low-dose supplementation protocol was used in the present study. The low dose vitamin D_3 supplementation protocol is in accordance with a dose, recommended by most of the aforementioned guidelines for older individuals (European Food Safety Authority, 2014; German Nutrition Society, 2012; Ross et al., 2011). The higher dose is oriented at a higher RDI suggestion by the Endocrine Society (Holick et al., 2011), following tentative evidence of higher vitamin D requirements among seniors in order to achieve better improvements in muscle function parameters (Bischoff-Ferrari et al., 2004). Another RDI recommendation for older adults is targeted at the Central European population and its range represents the two respective doses of the present study (Pludowski et al., 2018). The control group received a placebo instead of vitamin D3, but attended the training intervention to examine the possible additional effects of the vitamin D_3 supplementation on the training success.

2 Methods

This thesis is part of the NutriAging research project, a trans-border initiative between Austria and Slovakia, conducted by the University of Vienna and the Comenius University of Bratislava, which was funded by the European Union (INTERREG SK-AT). The project investigates the response of several health parameters to the supplementation of different nutrients combined with progressive resistance training. The observed effects on various outcome measures were separately evaluated by students of diverse fields of study (Wagner & Muchová, 2020). Data collected from the NutriAging vitamin D study, including questionnaires gathering information on health-related quality of life (SF-36) and back pain (RMDQ), has been used in this thesis.

2.1 General procedure

The vitamin D_3 intervention study was conducted as a randomized, placebo-controlled and double-blinded trial, examining elderly persons in 3 different groups simultaneously over a 16-week period. Participants were mobile, community-dwelling men and women, aged between 65 and 85 years. The subjects were assigned randomly to either a placebo-controlled group (CON) or to one of the two vitamin D_3 intervention cohorts, which differed in their supplementation protocols (dose and frequency). The study took place in 2019 between the months of February and July. Persons willing to participate were tested for eligibility by means of the inclusion and exclusion criteria at t0. Four weeks past t0, baseline data was collected and the nutritional interventions started (t1). Five weeks after baseline testing (t2), the progressive resistance training was implemented in all groups for the duration of 10 weeks. At the end of the study, data was collected for the last time (t3). Apart from the 3 main measuring points (t1, t2 and t3), serum 25(OH)D concentrations were quantified at three additional points: three, nine and thirteen weeks after t1 (Semmelmayer, 2020). The general procedure and time flow of the NutriAging vitamin D study are displayed in figure 2.

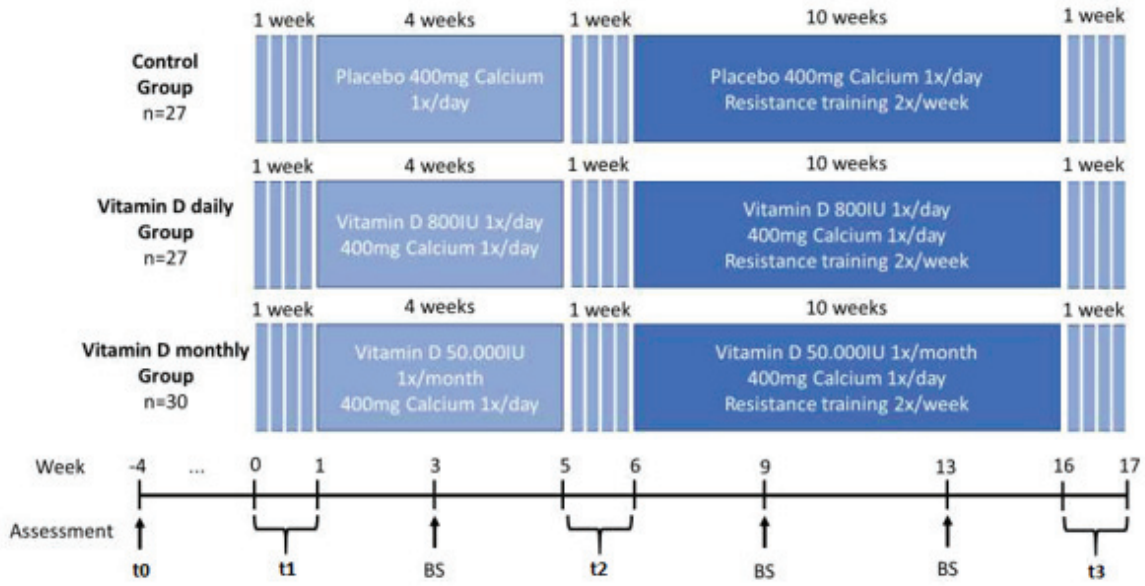

Figure 2: Study design.

2.2 Recruiting and inclusion/exclusion criteria

After reaching out to potential subjects through adverts in the media (newspapers, radio and internet), persons declaring interest to enter the study were provided with additional information on the project. They were asked to pass on information to other possible participants, such as friends or relatives. Single appointments with the study physician were scheduled (t0) for those subjects willing to participate at the University of Vienna, where they were tested for eligibility according to the inclusion/exclusion criteria.

To be included men and women had to be aged between 65 and 85 years, mobile (without any walking aids), community-dwelling and exceed a Mini-Mental-State test score of 23 (Folstein et al., 1975).

Subjects had to meet all inclusion criteria to be enrolled in the trial, while candidates were excluded as soon as one of the following exclusion criteria was met: vitamin D status higher than 30 ng/ml, chronic diseases contradicting resistance training, severe cardiovascular conditions (Williams et al., 2007), diabetic retinopathy, osteoporosis or osteopenia treated with vitamin D and/or calcium supplementation, renal diseases, pathological parathyroid hormone (PTH) levels, cardiac glycoside intake, diuretic (thiazide based) intake, pathological calcium levels, a frailty-index ≥ 3 (Fried et al., 2001), regular intake of cortisone (medication, antibiotics) in the last 6 months, regular resistance training (more than once per week) in the last 6 months and missing consent form. Accepted subjects had to give written informed consent, after the aims, procedures and possible risks were elucidated to them (Semmelmayer, 2020).

The study protocol, approved by the Ethics Committee of Vienna (reference number: 00405), followed Austrian legislation (Doctors Act, CISA, Data Protection Act) and was designed accordingly to ICH-GPC guidelines and the Declaration of Helsinki (World Medical Association, 2013). The trial has been registered at ClinicalTrials.gov (NCT04341818).

2.3 Randomization

Candidates meeting the inclusion criteria were first stratified into subgroups according to sex, age (65 to 69.9; 70 to 74.9; 75 to 79.9; 80 to ≤85 years) and baseline vitamin D status (< 20 ng/ml; 20 to 30 ng/ml). Since these factors can be confounding variables for most of the tested parameters, the subgroups were evenly assigned to the three study cohorts to minimize distorting influences on the results. Group allocation was conducted at t0 right after testing for eligibility, using the randomization tool of the Medical University of Graz (Institute for Medical Informatics, Statistics and Documentation).

2.4 Intervention

This study examined the effects of a combined intervention, consisting of nutritional supplementation and progressive resistance training, on various parameters related to the mental and physical health. During the first phase of the trial (from t1 to t2) solely consisted of a nutritional intervention to gain information on its isolated effects. A different vitamin D supplementation protocol was used for each of the three cohorts, while all of them received the same daily amount of calcium (400 mg). The vitamin D_3 daily group (VDD) received a lower daily dose (800 IU) of vitamin D_3 compared to the vitamin D_3 monthly group (VDM) with a higher monthly dosage (50000 IU) and CON was only administered the calcium supplement. The resistance training was implemented at t2 for all participants alike and would last 10 weeks, while the nutritional intervention continued with the same supplementation regimes (Semmelmayer, 2020).

2.4.1 Nutrition

The nutritional intervention, using vitamin D_3 (cholecalciferol) and calcium supplements, started at t1 after baseline data was collected and ended 16 weeks later at t3, when the post-intervention parameters were assessed. All three groups received 400 mg of calcium per day, but were administered different amounts of vitamin D_3. VDD obtained 800 IU of vitamin D_3 each day for the duration of the whole trial, resulting in an overall dose of 89600 IU vitamin D_3. Starting at baseline (t1), VDM was provided with four monthly doses, each containing 50000 IU of vitamin D_3, every four weeks, which resulted in an overall amount of 200000 IU of vitamin D_3 and equates to approximately 1786 IU per day. The

dosing for the VDD subjects was in accordance with several recommendations targeted at seniors (European Food Safety Authority, 2014; German Nutrition Society, 2012; Ross et al., 2011). The supplementation protocol in VDM was oriented on a recommendation, which suggested higher doses for this age group (Holick et al., 2011). The calcium supplement did function as the placebo for the control group.

Participants in VDD took the supplements autonomously, which were handed out in a box with 28 chambers, each containing the respective daily dosage of vitamin D_3. The study personnel administered the high doses of vitamin D_3 for VDM at baseline and during three follow-up examinations. Calcium supplements were produced by Mamisch GmbH Prorenal (Ludwigshafen, Germany). Vitamin D_3 supplements were used from Vitactiv Natural Nutrition, Feel Good Shop BV (Venlo, Netherlands) and from Gall-Pharma GmbH (Judenburg, Austria) for VDD and VDM respectively (Semmelmayer, 2020).

2.4.2 Training

The resistance training started in week 6 of the trial (after t2) and was conducted twice a week, with at least 48 hours of rest in between. The training intervention lasted 10 weeks, using the first two weeks as a progressive acclimation phase, continuously adapting intensities to individual performance levels. The participants attended two guided sessions (60 - 90 minutes per session) every week in small groups (≤ 5 persons), supervised by a sports science student.

After ten minutes of warm-up, including mobility and balance training, resistance training was performed using machines, bodyweight and free weights (dumbbells), even though most exercises were machine-guided (Technogym Selection Line 700 and 900). The intervention protocol stipulated the pairing of agonist and antagonist exercises, which were conducted in alternating supersets with a short break between each set. The sessions ended with five to ten minutes of cool-down-activities, involving stretching exercises with main focus on the upper back muscles.

The personnel kept track of repetition counts and the trainings were documented using training diaries, which were filled in after every set. Subjects rated each session's perceived intensity on the BORG scale, ranging from 0 (no exertion) to 10 (highest exertion).

The mixed exercises were selected in accordance to the recommendations on resistance training for older persons by the American College of Sports Medicine (Riebe et al., 2018) and the American Heart Association (Nelson et al., 2007). The exercise pairs can be found in table 3.

Table 3: Progressive resistance training intervention exercise pairs

Label	Exercise 1	Exercise 2
A1 & A2	Goblet Box Squat (FW)	Seated Leg Curls (MG)
B1 & B2	Seated Lat Pull-Down (MG)	Seated Shoulder Press (FW)
C1 & C2	Leg Press (MG)	Plank With Alternating Leg Raise (BW)
D1 & D2	Rowing Seated (MG)	Chest Press (MG)

FW (free weights); MG (machine-guided); BW (bodyweight)

The first week of the physical intervention was used to introduce the training routine to the participants. The study personnel informed the subjects about the correct execution of the exercises and proper usage of the machines, also pointing out the most commonly observed mistakes. The participants were instructed to perform the respective concentric movements of each exercise as fast as possible, while releasing the weight in a controlled manner over two to three seconds during the eccentric phases. In order to facilitate familiarization, weight resistances were kept rather low in these two sessions, using 40% to 50% of the estimated one repetition maximum with ten to twenty repetitions per set for each exercise. Starting weights for the first two sessions are given in table 4.

Table 4: Exercise starting weights for the first two sessions

Label	Exercise	Weight
A1	Goblet box squat	Women: 3 – 5 kg
		Men: 5 – 10 kg
A2	Sitting leg curl	15% Bodyweight
B1	Lat pull-down	25% Bodyweight
B2	Dumbbell shoulder press	Women: 2 – 5 kg
		Men: 3 – 5 kg
C1	Leg press	30% bodyweight
C2	Front plank with alternating leg raise	Hands placed on a bench/box,
		5 repetitions per leg
D1	Rowing	25% bodyweight
D3	Chest press	Women: 5 – 10 kg
		Men: 10 – 20 kg

Kg (kilogram)

The third session already included all eight exercises and subjects were asked to execute the training as autonomously as possible. If required, the supervising staff still provided assistance, as for all of the consecutive sessions. The participants conducted two sets of

each exercise and the resistances were set at approximately 50% to 70% of the 1RM with a repetition count of eight to twelve per set.

So far, the intensities had been oriented on an estimated 1RM. In order to adapt the training progression adequately for each subject, the fourth session was used to establish the individual five repetition maxima (5RM) with a test procedure following Nascimento et al. (2013) and Wood et al. (2001). To prevent injuries, the 5RM test was only performed using the machine-guided exercises, as the free-weight practises require a higher level of expertise and an adequate physical condition. Rowing was excluded from testing, since it exerts almost the same muscles as the lat pull-down. The resistances for the test were derived from the maximum performances (weight and repetitions) of the prior session, respective calculations were performed on the basis of a reference table (Haff & Triplett, 2016). Using the assessed 5RM values, analogue calculation created the new respective 1RM for each subject and was used in the oncoming intensification phase.

From the fifth training on, three sets were conducted each session, starting with 60% to 80% of the established 1RM, aiming for eight to twelve correct repetitions. Rowing intensity was derived from the 5RM of the lat pull-down. The training personnel administered the resistances for those exercises, which had not been included in the 5RM test, after inquiring the individually perceived exertion of the participants. Intensities for each exercise were increased, if a subject was able to exceed a repetition count of twelve in the first respective set of a session. Adjustments were conducted gradually, either switching to the next heavier dumbbell or adding one weight plate on the machines. Intensification of the plank was first achieved through an increase of leg raise repetitions, then by extending the lifting phase and eventually by lowering the height of the plank (Semmelmayer, 2020). The training progression is provided in figure 3.

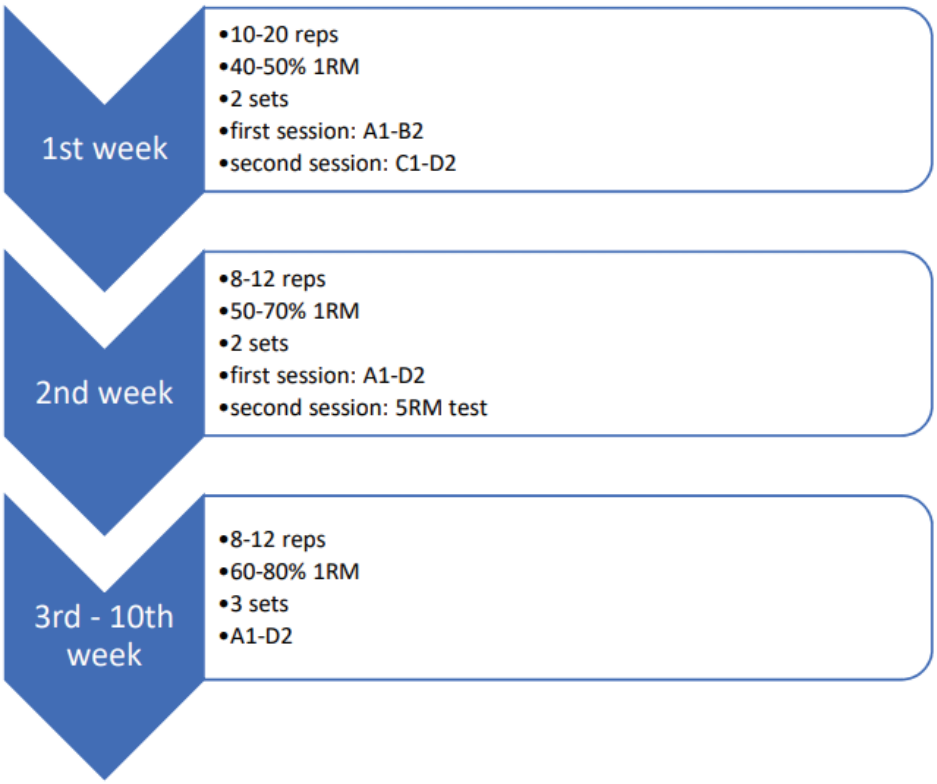

Figure 3: Training progression.

2.5 Outcomes

Apart from the anthropometric parameters height, bodyweight, body mass index (BMI), absolute muscle mass and relative fat mass, blood serum 25(OH)D concentrations as well as the SF-36 and RMDQ scores were analysed in this thesis. Questionnaires were first handed out at baseline (t1), then after the first intervention phase (t2) and finally after ten weeks of additional resistance training (t3). For the serum 25(OH)D concentration analysis, the means of the vitamin D levels assessed at t0 and t1 served as baseline values and the samples collected at t2 and t3 were used as mid- and post-intervention values respectively. Data on the anthropometrics was only used from the baseline assessment (t1) to identify pre-intervention group differences.

2.5.1 Anthropometric data

The anthropometrical testings were performed at t1, t2 and t3, after the participants were fasting over night. Shoes and heavy clothing were removed before measurements. Height [m] and bodymass [kg] were assessed using a combined medical weight (model 877, seca GmbH & Co. KG, Hamburg, Germany) and height scale (model 217, seca GmbH & Co. KG, Hamburg, Germany). Height was measured after subjects were instructed to straighten up and while touching the scale with their heels, gluteus, upper back and head. The BMI was derived from this data by means of the formula $\frac{bodymass\ [kg]}{height\ [m]^2}$.

A bioelectrical impedance analysis (BIA) with the InBody 3.0 body composition analyzer (InBody 3.0, Biospace, Chonan-si, South Korea) was used to quantify absolute lean body mass [kg] and body fat mass [kg]. Subjects were standing barefoot on the machine, holding the handles with extended arms at 20 degrees abduction. Contact points were moisturized in case of insufficient conductivity (Semmelmayer, 2020).

2.5.2 Serum 25(OH)D concentrations

The serum 25(OH)D concentrations were used as reference of the vitamin D status. In total, serum 25(OH)D concentrations were quantified seven times throughout the trial. The first assessment was conducted as part of the testings for eligibility at t0. In addition to the vitamin D level values obtained during the three main examinations at t1, t2 and t3, concentrations were measured three, nine and thirteen weeks after the start of the nutritional intervention. The collection of the venous blood samples was performed in the morning between 6:30 and 9:30 am, in a fasted condition. Z Serum Sep Clot Activator collection tubes (Vacuette, Greiner bio-one, Kremsmünster, Austria) were used to clot 8 ml of blood for a minimum of 30 minutes. Serum supernatant was extracted by centrifugation at room temperature for 10 minutes with a speed of 3000 rpm. Sample analysis was conducted by a routine laboratory (Dr. Claudia Vidotto, 1230 Vienna, Austria).

2.5.3 SF-36 questionnaire – Health-related quality of life

The German version of the SF-36 self-reported questionnaire was used to measure health-related quality of life in the study sample. The survey consists of 36 Likert-type questions, which can be categorized by eight sub-domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health. Respective scores, ranging from 0 to 100, are generated for each sub-domain. Two higher-order summary scores can be derived from the eight sub-scores, the physical component summary (PCS) score, representing the bodily domain, and the mental component summary (MCS) score, reflecting psychological aspects. Literature on the minimal clinically important difference (MCID) among older subjects regarding the SF-36 is limited. However, an indication can be found in an article of Samsa et al. (1999), suggesting that the MCID of the SF-36 scores lies between 3 and 5 points. Calculations of the scores were performed in accordance with developer specifications. Detailed information on the algorithms, used to generate the scores, can be found elsewhere (Grassi & Nucera, 2010; Taft et al., 2001).

2.5.4 Roland & Morris Disability Questionnaire – Back pain

Information on back pain was obtained through a German version of the Roland & Morris Disability Questionnaire (RMDQ), an outcome measure specified for low-back functionality (Wiesinger et al., 1999). The RMDQ form offers 24 statements describing impairments of every day life (e.g., walking, getting up, dressing, mood, appetite, sleep) caused by back pain. Each selected item represents one point of the total score ranging from 0 to 24 and the extent of disability increases along with the score. The RMDQ is easy to complete, capable of assessing differences in the severity of back pain and proved as a tool with high reliability, validity and sensitivity for change (Exner & Keel, 2000). Participants were asked to select each statement applying to their current condition.

2.6 Statistical analysis

Data of all enrolled participants was analysed, regardless of compliance, according to intention-to-treat analysis principles (McCoy, 2017).

Data was analysed with non-parametric statistical tests, since the questionnaire scores were on an ordinal scale.

Baseline differences in the distributions of sex and drop-outs among the groups were assessed using the Chi^2 test of homogeneity.

As the data was not tested for normal distribution, the Kruskal-Wallis H test was run to determine group-differences at the time points t1, t2 and t3. The Dunn's (1964) procedure was used for post hoc analysis performing pairwise comparisons with a Bonferroni correction for multiple comparisons. Within-group effects over time during the 16-week intervention were identified using the Friedman test in the total study sample and in each group respectively. For subsequent post hoc analysis pairwise comparisons were performed (SPSS Statistics, 2012) with a Bonferroni correction for multiple comparisons.

The Wilcoxon signed-rank test was used to determine differences in the two changes observed in the respective intervention phases, from t1 to t2 and from t2 to t3; it was run for each group and the total sample respectively.

Results of all statistical tests are compared to the χ^2-distribution and information on the degrees of freedom (df), asymptotic significances (p) and the values of the respective test-statistics is provided.

The results of the Chi^2 test of homogeneity include the obtained values of the Paerson Chi Square test statistic (χ^2) and are presented in the form of: (χ^2(df) = χ^2, p)

The results of the Kruskal-Wallis test include the obtained values of the H – statistic (H) and are presented in the form of: (χ^2(df) = H, p).

The results of the Friedman test include the obtained values of the Friedman test statistic (χ_w^2) and are reported in the form of: (χ^2(df) = χ_w^2, p).

Adjusted *p*-values are presented for the post hoc procedures of the Kruskal-Wallis and Friedman test performing Bonferroni corrected pairwise comparisons.

The results of the Wilcoxon test include the values of the standardized test statistic (Z) and are reported in the form of: (χ^2(df) = Z, p).

Significance was accepted at the $p < .05$ level for all statistical tests and pairwise comparisons.

The Pearson correlation coefficient (*r*) was used determining the effect sizes of the Wilcoxon test, using the formula $r = \left|\frac{z}{\sqrt{n}}\right|$, where n is the total number of observations on which Z is based (Fritz et al., 2012). Effect sizes were rated according to the classification of Cohen (1988), defining r values between .10 and .30 as a low effect, between .10 and .30 as a moderate effect and those bigger than .50 as a large effect.

Values in the tables are presented as median (minimum; maximum). Medians in the text are provided without minimum and maximum and are presented in the form of (*Mdn* = median), if not directly addressed.

Statistical analysis was performed using IBM SPSS Statistics v27 (IBM Corporation, New York, USA).

3 Results

3.1 Participant flow

Responding to advertising and open calls, 378 persons initially expressed interest in the trial. Eligibility was assessed for 231 persons, of which 131 were excluded, since 127 did not meet the inclusion criteria and four declined to participate. The other 100 persons were included in this trial and randomly allocated to three intervention groups (CON, VDD, VDM). At baseline, 33 persons were assigned to CON, 30 to VDD and 37 to VDM. All enrolled participants started the nutritional intervention at t1. Only the VDD group remained complete until follow-up after 6 weeks (t2), CON and VDM groups reported one and two drop-outs respectively, all due to loss of interest. The remaining 97 persons started with the training intervention at t2. At the end of both interventions, 12 more persons had dropped out of the study. Five drop-outs were observed in the CON group, three in the VDD group and four in the VDM group, all due to medical reasons. After 17 weeks 85 participants completed the study and were analysed, 27 (81.8%) in CON, 27 (90.0%) in VDD and 31 in VDM (83.8%). Detailed information on participants flow is given in figure 4.

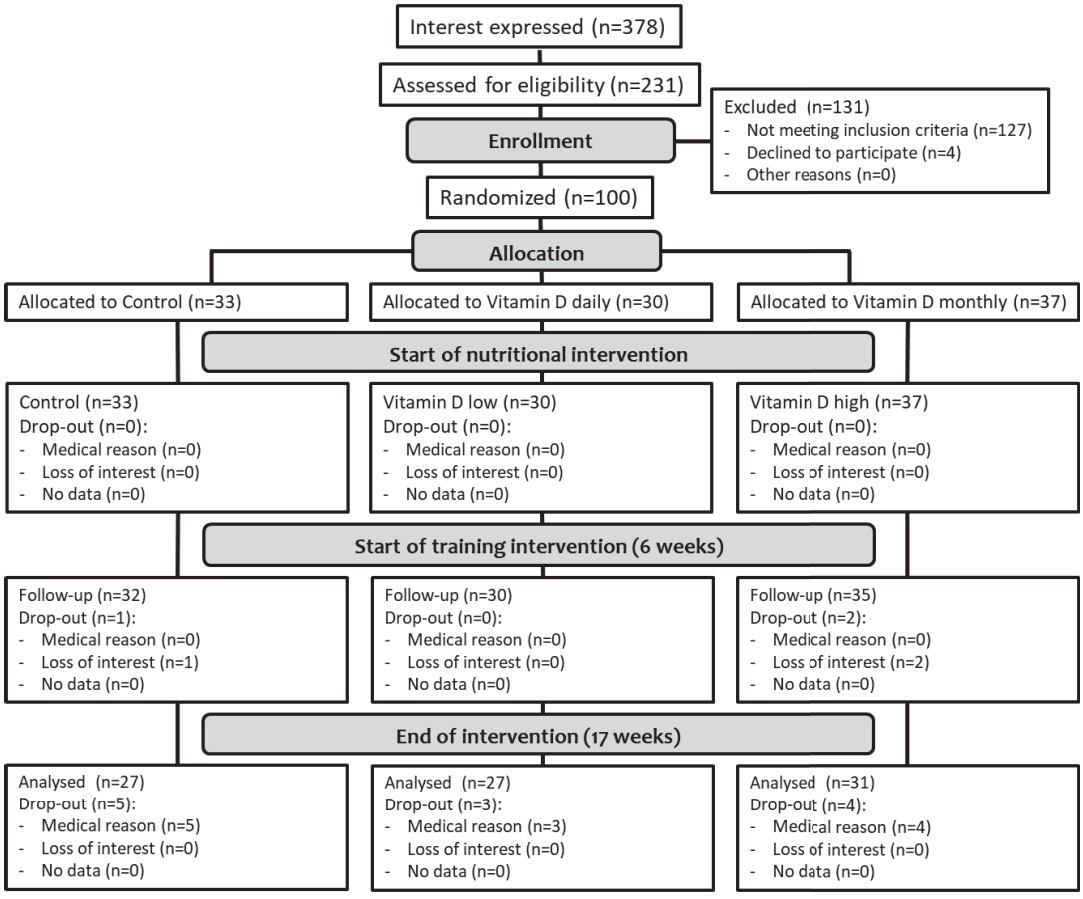

Figure 4: Participant flow.

3.2 Baseline characteristics

3.2.1 Anthropometrics and serum 25(OH)D concentrations

Data on sex, age, body mass, height, BMI and serum 25(OH)D concentrations was collected from all 100 persons enrolled in the study, whereas data on absolute muscle mass and relative body fat were only gathered from 98 participants, due to missing and implausible values. Median values, minimum, maximum and p-values are presented in table 5.

Table 5: Baseline anthropometrics and serum 25(OH)D concentrations

	total	CON	VDD	VDM	*p*-value
Sex [f/m] (%f), n=100	**33/67 (33.0% f)**	10/23 (30.3% f)	10/20 (33.3% f)	13/24 (35.1% f)	*.911*
Age [years], n=100	**69.3 (65.0 ; 85.0)**	68.9 (65.0 ; 85.0)	68.7 (65.3 ; 79.2)	69.9 (65.0 ; 80.9)	*.707*
Body mass [kg], n=100	**80.3 (49.4 ; 129.6)**	77.4 (49.4 ; 126.1)	85.8 (53.3 ;115.1)	80.3 (51.8 ; 129.6)	*.092*
Height [m], n=100	**1.73 (1.43 ; 1.94)**	1.73 (1.48 ; 1.92)	1.73 (1.57 ; 1.86)	1.73 (1.43 ; 1.94)	*.922*
BMI [kg/m²], n=100	**26.6 (19.3 ; 42.6)**	25.7 (19.3 ; 42.6)	27.2 (21.1 ; 38.1)	27.6 (19.7 ; 42.6)	*.040*
25(OH)D [ng/ml], n=100	**23.3 (11.7 ; 37.5)**	22.8 (12.0 ; 28.6)	23.8 (11.7 ; 35.0)	23.4 (12.5 ; 37.5)	*.521*
Muscle mass [kg], n=98	**55.9 (30.6 ; 82.8)**	53.7 (30.6 ; 82.8)	57.1 (38.5 ; 73.0)	55.9 (35.9 ; 75.5)	*.359*
Body fat [%], n=98	**26.1 (12.2 ; 50.4)**	25.3 (12.2 ; 43.5)	29.7 (14.2 ; 46.3)	26.3 (16.1 ; 50.4)	*.628*

Shown values: n = sample size; median (minimum ; maximum) for each group and the total sample; *p*-value: differences between groups (Chi^2 Test, Kruskal-Wallis Test).
CON (control group); VDD (vitamin D daily); VDM (vitamin D monthly); f (female); m (male); % (per cent); kg (kilogram); m (meter); BMI (body mass index); 25(OH)D (serum 25(OH)D concentration); ng/ml (nanogram per millilitre)

The entire study population consisted of 33 (33%) women and 67 (67%) men with a median age [years] of 69.3 (65.0 ; 85.0). Median body mass [kg] was 80.3 (49.4 ; 129.6), median height [m] was 1.73 (1.43 ; 1.94) and median BMI [kg/m²] was 26.6 (19.3 ; 42.6). Median serum 25(OH)D concentration [ng/ml] was 23.3 (11.7 ; 37.5), median muscle mass [kg] was 55.9 (30.6 ; 82.8) and median relative body fat mass [%] was 26.1 (12.2 ; 50.4).

The Chi^2 test of homogeneity was used to identify group-differences in the distributions of both sexes and the observed drop-outs. No expected cell frequencies were below 5. No statistically significant differences between groups were reported in the distributions of

female and male subjects ($\chi^2(2) = 0.186$, $p = .911$). Also, the number of drop-outs did not differ statistically significantly between the groups ($\chi^2(2) = 0.893$, $p = .640$).

The Kruskal-Wallis test showed no statistically significant differences between groups in median age ($\chi^2(2) = 0.694$, $p = .707$), body mass ($\chi^2(2) = 4.770$, $p = .092$), height ($\chi^2(2) = 0.162$, $p = .922$), 25(OH)D concentration ($\chi^2(2) = 1.303$, $p = .521$), absolute muscle mass ($\chi^2(2) = 2.051$, $p = .359$) and relative body fat mass ($\chi^2(2) = 0.931$, $p = .628$).

The median BMI values were statistically significantly different between the three groups ($\chi^2(2) = 6.442$, $p = .040$). The post hoc analysis did yet not reveal statistical significance for the pairwise comparisons of BMI values for any group combination ($p \geq .05$).

3.2.2 Baseline SF-36 scores

At t1, baseline values of the SF-36 questionnaire were collected from 99 participants; one person did not complete the questionnaire. Median scores, minima, maxima and p-values are given in table 6.

Table 6: Baseline SF-36 scores

	total	**CON**	**VDD**	**VDM**	***p*-value**
PCS, n = 99	**53 (30.8 ; 62.9)**	51.6 (33.7 ; 57.4)	52.8 (33.0 ; 58.7)	54.1 (30.8 ; 62.9)	*.467*
MCS, n = 99	**56.4 (22.9 ; 63.4)**	56.2 (22.9 ; 62.8)	57.3 (40.5 ; 62,9)	55.6 (26.6 ; 63.4)	*.601*
Physical functioning, n = 99	**95 (30 ; 100)**	90 (30 ; 100)	90 (60 ; 100)	95 (50 ; 100)	*.225*
Role-physical, n = 99	**100 (0 ; 100)**	100 (25 ; 100)	100 (0 ; 100)	100 (0 ; 100)	*.051*
Bodily pain, n = 99	**84 (22 ; 100)**	84 (41 ; 100)	84 (22 ; 100)	100 (32 ; 100)	*.379*
General health, n = 99	**77 (20 ; 100)**	77 (20 ; 92)	82 (47 ; 100)	77 (50 ; 100)	*.918*
Vitality, n = 99	**75 (10 ; 95)**	70 (15 ; 85)	75 (40 ; 95)	75 (10 ; 95)	*.191*
Social functioning, n = 99	**100 (37.5 ; 100)**	100 (37.5 ; 100)	100 (50 ; 100)	100 (50 ; 100)	*.761*
Role emotional, n = 99	**100 (0 ; 100)**	100 (0 ; 100)	100 (0 ; 100)	100 (33.3 ; 100)	*.185*
Mental health, n = 99	**84 (32 ; 100)**	84 (32 ; 100)	88 (56 ; 100)	84 (44 ; 100)	*.802*

n = 99; Shown values: n = sample size; median (minimum ; maximum) for each group and the total sample; *p*-value: differences between groups (Kruskal-Wallis H-Test). CON (control group); VDD (vitamin D daily); VDM (vitamin D monthly); PCS (SF-36 physical component summary); MCS (SF-36 mental component summary)

The median physical and mental component scores of the whole study population were 53 (30.8 ; 62.9) and 56.4 (22.9 ; 63.4) respectively. As assessed with the Kruskal-Wallis test, PCS did not differ statistically significantly between CON (n = 33), VDD (n = 29) and VDM (n =37) ($\chi^2(2) = 1.524$, p = .467). MCS also showed no statistically significant group differences at baseline ($\chi^2(2) = 1.018$, p = .601). The Kruskal-Wallis test did not identify statistically significant differences between the cohorts for any of the baseline SF-36 sub-scores.

3.2.3 Baseline Roland & Morris Disability Questionnaire scores

Baseline RMDQ scores were collected from 98 subjects, two persons did not fill in the questionnaires. The median score was 0 (0 ; 15) for the total study sample. The Kruskal-Wallis test did not identify any statistically significant group differences between CON (n = 33), VDD (n = 29) and VDM (n = 36) ($\chi^2(2) = 2.918$, p = .232).

Median scores, minima, maxima and p-values are given in table 7.

Table 7: Baseline Roland & Morris Disability Questionnaire scores

	total	**CON**	**VDD**	**VDM**	***p*-value**
RMDQ n=98	0 (0 ; 15)	0 (0 ; 7)	0 (0 ; 11)	0 (0 ; 15)	*.232*

Shown values: n = sample size; median (minimum ; maximum) for each group and the total sample; *p*-value: differences between groups (Kruskal-Wallis H-Test). CON (control group); VDD (vitamin D daily); VDM (vitamin D monthly); RMDQ (Roland-Morris Disability Questionnaire

3.3 SF-36 physical component summary

The Kruskal-Wallis test reported no statistically significant differences in PCS scores between the groups CON (n = 26), VDD (n = 25) and VDM (n = 31) for all three time points t1 ($\chi^2(2) = 4.091$, p = .129), t2 ($\chi^2(2) = 3.997$, p = .136) and t3 ($\chi^2(2) = 0.117$, p = .943).

The Friedman test did neither reveal statistically significant time effects for the total 82 subjects irrespective of group allocation ($\chi^2(2) = 0.043$, p = .979), nor for any of the three groups, CON ($\chi^2(2) = 0.951$, p = .621), VDD ($\chi^2(2) = 0.320$, p = .852) and VDM ($\chi^2(2) = 0.992$, p = .609).

The Wilcoxon test was run to determine if the changes in the PCS scores differed between the two intervention phases from t1 to t2 and from t2 to t3. There were no statistically significant differences observed in CON (z = 0.140, p = .889), VDD (z = -0.363, p = .716) or the total sample (z = -1.318, p = .188). In VDM, the difference in the changes did show statistical moderately between the two phases in VDM (z = -2.116, p = .034, r = .38). There was a median increase of the PCS from t1 to t2 (*Mdn* = 1.7) and a median decrease from t2 to t3 (*Mdn* = -1.2).

Median scores, minima, maxima and p-values are presented in table 8.

Table 8: Results SF-36 physical component summary scores

Parameter	Group	Time points			*Time effects*	Time point differences		*Group effects*
		t1	t2	t3		Δ (t2-t1)	Δ (t3-t2)	
Physical Component Summary	CON	51.5 (33.7 ; 57.4)	53.3 (38.8 ; 57.4)	51.6 (39.5 ; 58.5)	*.621*	0.4 (-8.1 ; 17.3)	0.6 (-15.6 ; 7.7)	*.889*
n = 82	VDD	52.8 (33.0 ; 58.7)	52.0 (40.8 ; 57.4)	52.5 (34.3 ; 61.8)	*.852*	-0.4 (-6.5 ; 9.6)	0.8 (-22.4 ; 8.7)	*.716*
	VDM	54.5 (42.1 ; 62.9)	54.5 (38.7 ; 67.9)	52.2 (26.2 ; 67.8)	*.609*	1.7 (-40.2 ; 9.1)	-1.2 (-22.4 ; 11.0)	*.034*
	total	**53.4 (33.0 ; 62.9)**	**53.1 (38.7 ; 67.9)**	**52.2 (26.2 ; 67.8)**	***.979***	**0.5 (-40.2 ; 17.3)**	**0.0 (-22.4 ; 11.0)**	***.188***
Group effects		*.129*	*.136*	*.943*				

Shown values: n = sample size; median (minimum ; maximum) for each group and the total sample for all respective time points; group effects: differences between groups for all respective time points (Kruskal-Wallis H-Test); differences between Δ (t2-t1) and Δ (t3-t2) for all groups and the total sample (Wilcoxon signed-rank Test); time effects: differences over all time points for each group and the total sample (Friedman Test).
CON (control group); VDD (vitamin D daily); VDM (vitamin D monthly)

3.4 SF-36 mental component summary

The Kruskal-Wallis test showed, that the median mental component scores did not differ statistically significantly between the groups CON (n = 26), VDD (n = 25) and VDM (n = 31) at all three time points t1 ($\chi^2(2) = 0.295$, p = .863), t2 ($\chi^2(2) = 1.252$, p = .535) and t3 ($\chi^2(2) = 4.906$, p = .086). The Friedman test identified no statistically significant differences over time during the intervention period for CON ($\chi^2(2) = 1.107$, p = .575) and VDD ($\chi^2(2) = 0.560$, p = .756), as well as for the whole sample size irrespective of group allocation ($\chi^2(2) = 2.779$, p = .249). For VDM it revealed a statistically significant general time effect from t1 (*Mdn* = 56.4), to t2 (*Mdn* = 56.9), to t3 (*Mdn* = 58.3) ($\chi^2(2) = 6.163$, p = .043). However post hoc analysis did not determine statistical significance for the pairwise comparisons of the periods from t1 to t2 (p = .197), t2 to t3 (p = 1.000) or t1 to t3 (p = .056).

Respective change rates of MCS during the two intervention phases were compared with the Wilcoxon test. It did not show any statistically significant differences, neither for CON (*z* = 0.267, p = .79), VDD (z = 0.713, p = .476), VDM (z = 0.137, p = .891) nor for the total 82 persons analysed (z = 0.668, p = .504). Median scores, minima, maxima and p-values are presented in table 9.

Table 9: Results SF-36 mental component summary

Parameter	Group	Time points			*Time effects*	Time point differences		*Group effects*
		t1	t2	t3		Δ (t2-t1)	Δ (t3-t2)	
Mental Component Summary	CON	56.0 (22.9 ; 62.8)	56.7 (23.4 ; 63.0)	56.4 (39.1 ; 62.4)	*.575*	-0.3 (-7.8 ; 9.8)	0.8 (-8.3 ; 15.8)	*.790*
n = 82	VDD	57.0 (40.5 ; 62.9)	55.9 (45.0 ; 61.2)	56.5 (42.9 ; 60.6)	*.756*	-0.1 (-4.7 ; 21.0)	-0.3 (-7.2 ; 12.4)	*.476*
	VDM	56.4 (26.6 , 63.4)	56.9 (15.0 ; 63.1)	58.3 (14.0 ; 67.4)	***.046***	-0.2 (-12.2 ; 12.6)	0.7 (-12 ; 26.4)	*.891*
	total	**56.4 (22.9 ; 63.4)**	**56.6 (15 ; 63.1)**	**56.9 (14.0 ; 67.4)**	***.249***	**-0.1 (-12.2 ; 21.0)**	**0.7 (-12 ; 26.4)**	***.504***
Group effects		*.863*	*.535*	*.086*				

Shown values: n = sample size; median (minimum ; maximum) for each group and the total sample for all respective time points; group effects: differences between groups for all respective time points (Kruskal-Wallis H-Test); differences between Δ (t2-t1) and Δ (t3-t2) for all groups and the total sample (Wilcoxon signed-rank Test); time effects: differences over all time points for each group and the total sample (Friedman Test). CON (control group); VDD (vitamin D daily); VDM (vitamin D monthly)

3.5 SF-36 sub-domains

For the 82 subjects analysed in the sub-domain physical functioning, the Kruskal-Wallis test showed statistically significant general group differences at t1 between CON (n = 27), VDD (n = 25) and VDM (n = 31) ($\chi^2(2) = 6.645$, p = .036). But post hoc comparisons did not reach significance for any group combination (p > .05).

In CON, the Friedman test identified a statistically significant general time effect in the physical functioning sub-domain from t1 (*Mdn* = 95), to t2 (*Mdn* = 95), to t3 (*Mdn* = 100) ($\chi^2(2) = 13.081$, p = .001). Post hoc analysis did reveal a statistically significant increase between t1 and t3 (p = .008), but the changes between t1 and t2 (p = .403) and between t2 and t3 (p = .403) did not meet significance levels. A significant overall time effect for this sub-domain was also reported for the whole study sample ($\chi^2(2) = 7.668$, p = .022), post hoc analysis however did not reveal any statistically significant pairwise comparisons of phases t1 to t2 (p = 1.000), t2 to t3 (p = .643) and t1 to t3 (p = .098). The other tests did not report any significant results for this sub-domain (p > .05).

Regarding the sub-domain role-physical, the Friedman and Kruskal-Wallis test did not determine any statistically significant results (p > .05).

The Wilcoxon test showed a statistically significant difference between the two changes of the respective intervention phases, ∆ (t2-t1) (*Mdn* = 0) and ∆ (t3-t2) (*Mdn* = 0) in the VDD (n = 25) group (z = -2.040, p = 0.41). The calculated effect size was moderate with r = .41.

Statistically significant effects over time could be observed for the sub-domain mental health in the VDM group (n = 31) and the total sample (n = 83), determined by the Friedman test. The VDM group showed a significant general time effect from ($\chi^2(2) = 8.420$, p = .015). Post hoc analysis identified the increase from t1 to t3 as statistically significant (p = .028). Pairwise comparisons did not reveal statistical significance for the changes from t1 to t2 (p = .487) or from t2 to t3 (p = .683). The total sample of 83 persons reported a statistically significant general time effect over the whole duration ($\chi^2(2) = 8.399$, p = .015). Post hoc analysis identified the increase from t1 to t3 (p = .025) to be responsible for this significant result, since the changes from t1 to t2 (p = .687) and from t2 to t3 (p = .453) did not reach the statistical significance level. No other statistically significant results were reported for this sub-domain by any of the statistical tests (p > .05).

The sub-domains general health, bodily pain, vitality, social functioning and role-emotional did not report any statistically significant results for all of the tests (p > .05).

Median scores, minima, maxima and p-values for all SF-36 results are presented in table 10

Table 10: Results SF-36 sub domains

Parameter	Group	Time points t1	t2	t3	*Time effect*	Time point differences Δ (t2-t1)	Δ (t3-t2)	*Group effect*
Physical functioning	CON	95 (30 ; 100)	95 (50 ; 100)	100 (60 ; 100)**	***.001***	0 (-20 ; 20)	0 (-10 ; 25)	*.832*
n = 82	VDD	90 (60 ; 100)	95 (50 ; 100)	95 (65 ; 100)	*.305*	0 (-10 ; 20)	0 (-15 ; 15)	*.702*
	VDM	95 (60 ; 100)	95 (70 ; 100)	95 (55 ; 100)	*.892*	0 (-20 ; 15)	0 (-40 ; 25)	*.458*
	total	**95 (30 ; 100)**	**95 (50 ; 100)**	**95 (55 ; 100)**	***.022***	**0 (-20 ; 20)**	**0 (-40 ; 25)**	***.491***
Group effect		***.036***	*.387*	*.676*				
Role physical	CON	100 (25 ; 100)	100 (0 ; 100)	100 (25 ; 100)	*.223*	0 (-25 ; 0)	0 (-75 ; 25)	*.750*
n = 83	VDD	100 (0 ; 100)	100 (75 ; 100)	100 (0 ; 100)	*.223*	0 (-25 ; 75)	0 (-100 ; 25)	*.041*
	VDM	100 (25 ; 100)	100 (0 ; 100)	100 (0 ; 100)	*.347*	0 (-75 ; 50)	0 (-50 ; 75)	*.530*
	total	**100 (0 ; 100)**	**100 (0 ; 100)**	**100 (0 ; 100)**	***.118***	**0 (-75 ; 75)**	**0 (-100 ; 75)**	***.122***
Group effect		*.203*	*.960*	*.813*				
Bodily pain	CON	74 (41 ; 100)	84 (51 ; 100)	73 (41 ; 100)	*.896*	0 (-26 ; 38)	0 (-43 ; 21)	*.778*
n = 83	VDD	84 (22 ; 100)	84 (31 ; 100)	84 (22 ; 100)	*.881*	0 (-31 ; 62)	0 (-59 ; 43)	*.768*
	VDM	100 (51 ; 100)	100 (51 ; 100)	100 (22 : 100)	*.520*	0 (-48 ; 22)	0 (-78 ; 48)	*.185*
	total	**84 (22 ; 100)**	**84 (31 : 100)**	**84 (22 ; 100)**	***.619***	**0 (-48 ; 62)**	**0 (-78 ; 48)**	***.340***
Group effect		*.069*	*.119*	*.257*				
General health	CON	77 (20 ; 92)	77 (30 ; 97)	82 (52 ; 100)	*.493*	0 (-30 ; 20)	0 (-10 ; 35)	*.572*
n = 84	VDD	74.5 (47 ; 100)	77 (47 ;97)	77 (47 ; 100)	*.580*	0 (-20 ; 25)	0 (-15 ; 30)	*.780*
	VDM	82 (50 ; 100)	82 (30 ; 100)	77 (57 ; 100)	*.076*	5 (-30 ; 30)	0 (-32 ; 35)	*.051*
	total	**77 (20 ;100)**	**77 (30 ; 100)**	**77 (47 ; 100)**	***.239***	**0 (-30 ; 30)**	**0 (-32 ; 35)**	***.421***
Group effect		*.525*	*.157*	*.924*				

Parameter	Group	Time points			*Time effect*	Time point differences		*Group effect*
		t1	t2	t3		Δ (t2-t1)	Δ (t3-t2)	
Vitality	CON	70 (15 ; 85)	72.5 (25 ; 95)	75 (40 ; 95)	*.449*	0 (-15 ; 20)	0 (-25 ;15)	*.290*
n = 83	VDD	75 (40 ; 95)	70 (50 ; 85)	70 (50 ; 95)	*.397*	0 (-25 ; 25)	0 (-15 ; 20)	*.442*
	VDM	75 (10 ; 95)	80 (15 ; 100)	80 (40 ; 100)	*.434*	5 (-35 ; 30)	0 (-30 ; 35)	*.973*
	total	**75 (10 ; 95)**	**75 (15 ; 100)**	**75 (40 ; 100)**	***.756***	**0 (-35 ; 30)**	**0 (-30 ; 35)**	***.829***
Group effect		*.156*	*.143*	*.182*				
Social functioning	CON	100 (37.5 ; 100)	100 (50 ; 100)	100 (62.5 ; 100)	*.140*	0 (-37.5 ; 25)	0 (-12.5 ; 37.5)	*.777*
n = 83	VDD	100 (50 ; 100)	100 (62.5 ; 100)	100 (75 ; 100)	*.676*	0 (-12.5 ; 25)	0 (-25 ; 25)	*.739*
	VDM	100 (50 ; 100)	100 (25 ; 100)	100 (25 ; 100)	*.727*	0 (-75 ; 37.5)	0 (-12.5 ; 37.5)	*.309*
	total	**100 (37.5 ; 100)**	**100 (25 ; 100)**	**100 (25 ; 100)**	***.229***	**0 (-75 ; 37.5)**	**0 (-25 ; 37.5)**	***.332***
Group effect		*.427*	*.717*	*.979*				
Role-emotional	CON	100 (0 ; 100)	100 (33.3 ; 100)	100 (66.7 ; 100)	*.196*	0 (-33.3 ; 66.7)	0 (-33.3 ; 33.3)	*.137*
n = 83	VDD	100 (0 ; 100)	100 (66.7 ; 100)	100 (33.3 ; 100)	*.223*	0 (0 ; 66.7)	0 (-33.3 ; 33.3)	*.066*
	VDM	100 (33.3 ; 100)	100 (0 ; 100)	100 (0 ; 100)	*.965*	0 (-66.7 ; 66.7)	0 (-66.7 ; 66.7)	*.905*
	total	**100 (0 ; 100)**	**100 (0 ; 100)**	**100 (0 ; 100)**	***.709***	**0 (-66.7 ; 66.7)**	**0 (-66.7 ; 66.7)**	***.968***
Group effect		*.659*	*.544*	*.685*				
Mental health	CON	80 (32 ; 100)	86 (28 ; 100)	84 (56 ; 100)	*.061*	0 (-28 ; 24)	2 (-20 ; 28)	*.706*
n = 83	VDD	86 (56 ; 100)	84 (52 ; 100)	84 (56 ; 96)	*.925*	0 (-16 ; 24)	0 (-24 ; 16)	*.585*
	VDM	84 (52 ; 100)	84 (44 ; 100)	92 (56 ; 100)*	***.015***	4 (-40 ; 16)	0 (-12 ; 32)	*.509*
	total	**84 (32 ; 100)**	**84 (28 ; 100)**	**88 (56 ; 100)***	***.015***	**0 (-40 ; 24)**	**0 (-24 ; 32)**	***.650***
Group effect		*.832*	*.772*	*.063*				

Shown values: n = sample size; median (minimum ; maximum) for each group and the total sample for all respective time points; group effects: differences between groups for all respective time points (Kruskal-Wallis H-Test); differences between Δ (t2-t1) and Δ (t3-t2) for all groups and the total sample (Wilcoxon signed-rank Test); time effects: differences over all time points for each group and the total sample (Friedman Test), significance levels for differences to t1 are marked next to minima and maxima: *(p ≤ .05), **(p ≤ .01), ***(p ≤ .001). CON (control group); VDD (vitamin D daily); VDM (vitamin D monthly)

3.6 Roland & Morris Disability Questionnaire scores

The Kruskal-Wallis test revealed statistically significant general group differences for CON (n =26), VDD (n = 26) and VDM (n = 30) at t1 ($\chi^2(2) = 7.852$, p = .020). The post hoc analysis showed statistically significant differences in the RMDQ scores between VDD (*Mdn* = 0) and VDM (*Mdn* = 0) (p = .043), but not between CON (*Mdn* = 0) and VDD (p = 1.000) or CON and VDM (p = 0.57). Groups did not differ statistically significantly at the other time points t2 ($\chi^2(2) = 4.570$, p = .102), and t3 ($\chi^2(2) = 2.068$, p = .355).

The Friedman test did not determine any statistically significant general time effects of the RMDQ scores, neither for the total 82 cases without regard of group allocation ($\chi^2(2) = 3.267$, p = .195), nor for any of the groups CON ($\chi^2(2) = 3.353$, p = .187), VDD ($\chi^2(2) = 4.606$, p = .100) and VDM, ($\chi^2(2) = 2.435$, p = .296).

The comparison of the change rates of the RMDQ scores during the two intervention phases, using the Wilcoxon test, did not reveal significant differences in any of the three groups CON (z = -1.544, p = .123), VDD (z = -0.563, p = .574) and VDM (z = 0.931, p = .352) and in the whole sample respectively (z = -1.561, p = .118). Median scores, minima, maxima and p-values are presented in table 11.

Table 11: Results Roland & Morris Disability Questionnaire

Parameter	Group	Time points			Time effects	Time point differences		Group effects
		t1	t2	t3		Δ (t2-t1)	Δ (t3-t2)	
RMDQ	CON	0 (0 ; 7)	0 (0 ; 12)	0 (0 ; 9)	*.187*	0 (-3 ; 6)	0 (-3 ; 5)	*.123*
n = 82	VDD	0 (0 ; 11)	0 (0 ; 9)	0 (0 ; 12)	*.100*	0 (-2 ; 2)	0 (-5 ; 12)	*.574*
	VDM	0* (0 ; 15)	0 (0 ; 13)	0 (0 ; 7)	*.296*	0 (-2 ; 7)	0 (-13 ; 7)	*.352*
	total	**0 (0 ; 15)**	**0 (0 ; 13)**	**0 (0 ; 12)**	***.195***	**0 (-3 ; 7)**	**0 (-13 ; 12)**	***.118***
Group effects		*.020*	*.102*	*.355*				

Shown values: n = sample size; median (minimum ; maximum) for each group and the total sample for all respective time points; group effects: differences between groups for all respective time points (Kruskal-Wallis H-Test); differences between Δ (t2-t1) and Δ (t3-t2) for all groups and the total sample (Wilcoxon signed-rank Test); time effects: differences over all time points for each group and the total sample (Friedman Test).
CON (control group); VDD (vitamin D daily); VDM (vitamin D monthly), RMDQ (Roland & Morris Disability Questionnaire)

3.7 Blood serum 25(OH)D concentrations

The cohorts CON (n = 27), VDD (n = 27) and VDM (n = 31) did not differ statistically significantly at time points t1 ($\chi^2(2) = 1.270$, p = .530) and t2 ($\chi^2(2) = 5.696$, p = .058), as assessed with the Kruskal-Wallis test. Significant general group differences were determined at t3 ($\chi^2(2) = 13.845$, p < .001). Pairwise comparisons of the cohorts identified a significant difference between CON (*Mdn* = 23.7 ng/ml) and VDM (*Mdn* = 32.7ng/ml) (p = .001), but neither between CON and VDD (*Mdn* = 29.0 ng/ml) (p = .262) nor between VDD and VDM (p = .155).

Median concentrations, minima, maxima and p-values are presented in table 12. The relative distributions of vitamin D deficiency, insufficiency and sufficiency in the study population at the respective timepoints are displayed in figure 5.

Table 12: Results serum 25(OH)D concentrations

Parameter	Group	Time points			Time effects	Time point differences		Group effects
		t1	t2	t3		Δ (t2-t1)	Δ (t3-t2)	
25(OH)D [ng/ml]	CON	21.7 (12 ; 28.6)	22.1 (11.9 ; 34.0)	23.7 (4.7 ; 52.5)	*.097*	0.3 (-6.2 ; 9.5)	1.3 (-11.2 ; 22)	*.058*
n = 85	VDD	23.7 (11.7 ; 35.0)	24.2 (13.6 ; 36.3)	29.0 (12.1 ; 39.6)**	*< .001*	1.3 (-17 ; 11.2)	3.8 (-6.7 ; 17.8)	*.212*
	VDM	23.4 (12.5 ; 37.5)	26.0 (15.7 ; 32.8)	32.7** (14.6 ; 49.1)***	*< .001*	3.1 (-13.2 ; 9.2)	6.6 (-16.3 ; 19.6)	*.003*
	total	**23.3 (11.7 ; 37.5)**	**23.8 (11.9 ; 36.3)**	**28.9 (4.7 ; 52.5)*** **	***< .001***	**1.3 (-17 ; 11.2)**	**4.4 (-16.3 ; 22)**	***< .001***
Group effects		.530	.058	**< .001**				

Shown values: n = sample size; median (minimum ; maximum) for each group and the total sample for all respective time points; group effects: differences between groups for all respective time points (Kruskal-Wallis H-Test), significance levels of differences to CON are marked next to medians: *(p ≤ .05), **(p ≤ .01), ***(p ≤ .001); differences between Δ (t2-t1) and Δ (t3-t2) for all groups and the total sample (Wilcoxon signed-rank Test); time effects: differences over all time points for each group and the total sample (Friedman Test), significance levels for differences to t1 are marked next to minima and maxima: *(p ≤ .05), **(p ≤ .01), ***(p ≤ .001). CON (control group); VDD (vitamin D daily); VDM (vitamin D monthly); 25(OH)D (serum 25(OH)D concentrations); ng/ml (nanogram per millilitre)

In general, median serum 25(OH)D concentrations continuously rised for all groups from each time point to the next. In contrast to the other groups, the Friedman test did not identify these differences as statistically significant in CON ($\chi^2(2) = 4.667$, $p = .097$). Looking at VDD, vitamin D levels showed a statistically significant general time effect from t1 (*Mdn* = 23.7 ng/ml), to t2 (*Mdn* = 24.2 ng/ml), to t3 (*Mdn* = 29.7 ng/ml) ($\chi^2(2) = 14.000$, $p = .002$). Pairwise comparisons revealed significant increases from t1 to t3 ($p = .001$) and from t2 to t3 ($p = .043$), but not from t1 to t2 ($p = .622$). The VDM group showed a significant general time effect in 25(OH)D concentrations from t1 (*Mdn* = 23.4 ng/ml), to t2 (*Mdn* = 26.0 ng/ml), to t3 (*Mdn* = 32.7 ng/ml) ($\chi^2(2) = 35.871$, $p < .001$). Post hoc analysis determined statistical significance for the increases from t1 to t3 ($p < .001$) and t2 to t3 ($p < .001$), but not for this from t1 to t2 ($p = .226$). The total sample's median 25(OH)D concentrations showed a significant general time effect from t1 (*Mdn* = 23.3 ng/ml), to t2 (*Mdn* = 23.8 ng/ml), to t3 (*Mdn* = 28.9 ng/ml) ($\chi^2(2) = 48.094$, $p < .001$). Bonferroni corrected pairwise comparisons reported significant increases from t1 to t3 ($p < .001$) and from t2 to t3 ($p < .001$), but not from t1 to t2 ($p = .138$).

Comparing differences between the two study phases, the Wilcoxon test did not reveal any statistically significant differences in the 25(OH)D level change rates of the respective intervention phases for CON ($z = 1.898$, $p = .058$) and VDD ($z = 1.249$, $p = .212$). In VDM the median increased from t1 to t2 (*Mdn* = 3.1 ng/ml) and from t2 to t3 (*Mdn* = 6.6 ng/ml) showed a significant difference ($z = 2.959$, $p = .003$). A large effect strength was reported ($r = .53$)

In the total sample, the respective change rates for the intervention phases also differed significantly ($z = 3.665$, $p < .001$). A moderate effect strength was observed ($r = .40$). The median increases were 1.4 ng/ml from t1 to t2 and 4.4 ng/ml from t2 to t3.

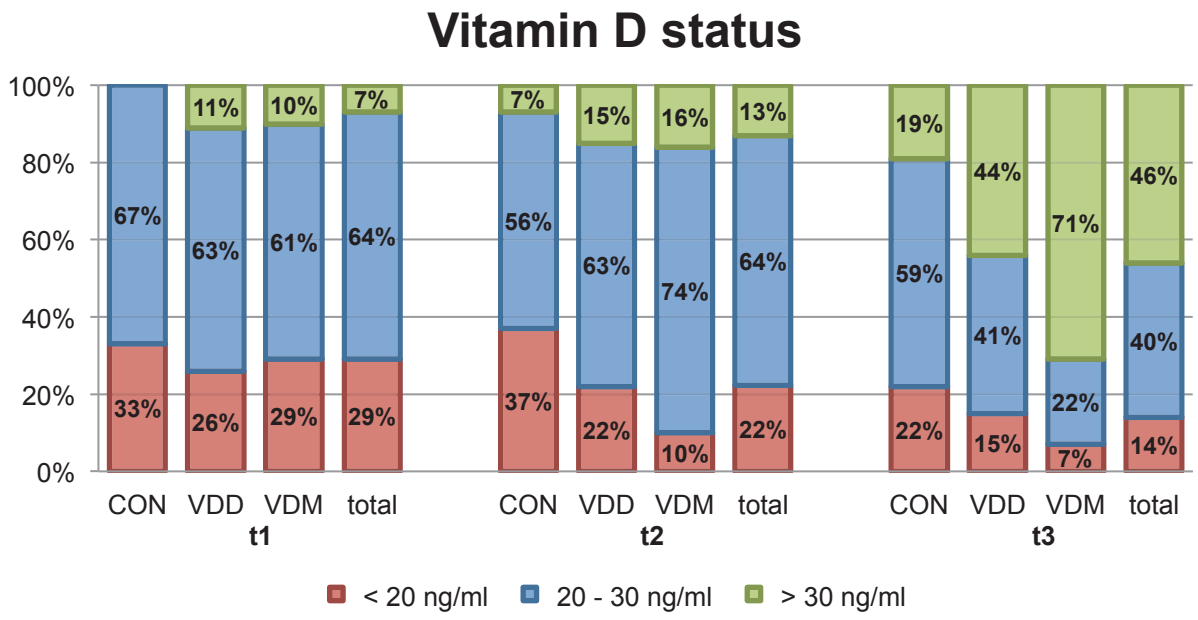

Figure 5: Relative vitamin D status distributions.

4 Discussion

The present study aimed to assess the efficacy of progressive resistance training and vitamin D_3 supplementation to improve the HRQoL (physical and mental function) and perceived disability created by LBP (RMDQ) in a population of healthy community dwelling older subjects. The progressive resistance training showed no effects on the two main outcome measures. Improvements in the mental scales MCS and mental health of the SF-36 were observed over the whole study duration in response to the higher-dose (50000 IU/month), but not the lower-dose (800 IU/day) vitamin D_3 protocol. Additional changes related to the vitamin D_3 intervention were observed neither in the remaining HRQoL scales nor in the RMDQ scores. The control group reported an increase in the SF-36 sub-scores of the domain physical functioning from baseline to post-intervention, which could have not been attributed to the progressive resistance training. The prevalence of self-reported disability caused by LBP increased in the study population from 21% at baseline to 24% post-intervention.

4.1 SF-36 scores

The HRQoL did not improve in response to the exercise intervention, although the efficacy of PRT in this context is well-documented by several meta-analyses (Cheema et al., 2014; Giuliano et al., 2017; Hart & Buck, 2019; Sieczkowska et al., 2020). Two factors explaining the missing effects in the present study might be the relatively short training period and the good health status, which was initially reported by the participants. Regarding duration, the aforementioned meta-analyses mostly included trials with an intervention phase exceeding ten weeks. Further, two of these reviews explicitly reported a positive relationship between the length of intervention and the improvements in the mental and physical quality of life (Hart & Buck, 2019; Sieczkowska et al., 2020). However, the lacking efficacy of PRT in the present trial cannot be related to the training duration solely, but might have also been influenced by the participants' initial levels of HRQoL. Previous research among elderly individuals has shown that the same (Levinger et al., 2007) or a even shorter exercise period (Socha et al., 2016) can lead to significant increases in the mental and physical quality of life dimensions. Both of these trials reported lower baseline SF-36 scores than observed in the present study population, which might alleviate the detection of improvements. Levinger et al. (2007) investigated the effects of PRT on mental and physical quality of life domains among subjects with either a low or high number of metabolic risk factors. A beneficial training effect on HRQoL was reported in the high-risk cohort only, which showed decreased basal SF-36 scores compared to the low-risk intervention group. Further, two longer studies did not observe improved quality of life in response to PRT among healthy older subjects, who reported high HRQoL pre-intervention (Matthews et al., 2020; Nicholson et al., 2015). These

two trials excluded candidates suffering from serious chronic conditions, which had been associated with impaired quality of life (Alonso et al., 2004). Severe disorders potentially limit the capacity to participate in the exercise program and were also among the exclusion criteria of the present study. Subsequently, the subjects showed higher baseline MCS and especially PCS scores compared to the norms for a general population of this age group, which were provided by the developers of the SF-36 questionnaire (Ware et al., 1994). The possible influences of the training duration and initial health status on the efficacy of PRT is promoted by the comparison of the present trial to another study with a mixed nutritional and exercise intervention (Berens et al., 2018). The participants in the RCT of Berens et al. (2018) reported lower baseline SF-36 scores and achieved significant increases in the mental HRQoL in response to a prolonged training program (6 months).

Considering the sound self-reported health at baseline among the subjects of the present study, the observed beneficial influence of the higher dosed vitamin D_3 regime seems quite surprising. According to a meta-analysis (Hoffmann et al., 2015) low to moderate effects on HRQoL may be achieved through vitamin D supplementation, but rather in diseased than in healthy study populations. The good health status of the participants of the present study is also displayed by the relatively high basal serum 25(OH)D concentrations, since vitamin D deficiency is generally associated with decreased HRQoL (Chao et al., 2014; Ecemis & Atmaca, 2013; H. J. Kim et al., 2015; Palazzo et al., 2019; Runia et al., 2015). Further, elevated vitamin D levels dampen the serum 25(OH)D concentration response to supplementation, impeding the acquisition of a higher vitamin D status (Mazahery & Von Hurst, 2015). Yet, the validity of the increases in mental HRQoL observed in the present study has to be put in perspective, since there are three points rendering them inconclusive. Firstly, no significant group differences were observed at any time point in the MCS and mental health scores. Secondly, the relation of the changes in vitamin D status and mental quality of life was not investigated irrespective of group allocation in this thesis, which should be performed to verify their association. And thirdly, improvements of clinical relevance, which are considered as score-changes of three or higher (Samsa et al., 1999), were reported for VDM in the sub-domain mental health only, but not in the MCS.

Nevertheless, the present study provides tentative evidence for the efficacy of vitamin D_3 supplementation to improve some psychological domains of the SF-36. Resembling increases of the mental HRQoL were reported in the RCT of Ramly et al. (2014), although within a longer intervention period. After one year of high-dose vitamin D_3 supplementation the scores of the MCS and the mental sub-domain vitality were significantly increased among the intervention subjects compared to placebo. They achieved average post-intervention serum 25(OH)D concentrations similar to those detected in VDM and also lacked improvements in the physical HRQoL domain. These findings suggest that the mental

domain might react earlier on rising serum vitamin D levels than the physical dimension. Increased serum 25(OH)D concentrations still result in higher mental HRQoL, according to the results observed in the one-year trial of Gugger et al. (2019). They compared the effects of three different intervention protocols on the mental health dimension of the SF-36 among 200 community-dwelling adults, aged 70 years or older. The best outcomes were achieved by the subjects within the highest quartile of the post-intervention serum 25(OH)D concentrations, irrespective of the supplementation regime.

A higher response in the average vitamin D status to the supplementation might have been necessary to obtain beneficial effects on the physical quality of life scores in the present study. According to the trial of Bischoff-Ferrari et al. (2004) enhanced physical functioning outcomes, which are relatable to the physical HRQoL domains, are achieved with higher serum 25(OH)D concentrations. Although VDM and VDD both reached median vitamin D levels within the recommended range of Bischoff-Ferrari et al. (2004), they still might have been too low to create detectable results. This proposition is supported by two other studies (Costan et al., 2014; Yilmaz et al., 2016), which reported significant improvements in the physical quality of life along with a substantially higher post-intervention vitamin D status than the subjects in the present study. Yilmaz et al. (2016) even observed highly statistically significant improvements in all SF-36 sub-domains. After the supplementation period, both trials reported serum 25(OH)D concentrations exceeding the suggested range of Bischoff-Ferrari et al. (2004). It seems difficult to determine the exact dose, which would have led to a comparable vitamin D status in the present study. Looking at the overall dose, Costan et al. (2014) used a five times higher dosage and Yilmaz et al. (2016) used the threefold amount compared to VDM. Yet, in another four month trial among elderly subjects (Gepner et al., 2012) a 40% higher vitamin D_3 supplementation protocol than the regime in VDM still created average vitamin D levels similar to the aforementioned studies. Looking at these variances, the most reliable way to increase vitamin D levels seems to be the use of 25(OH)D_3 as a supplement, especially within short intervention periods. It usually generates faster rises in serum 25(OH)D concentrations, which was proven by previous trials (Bischoff-Ferrari et al., 2012; Cashman et al., 2012; Vaes et al., 2018).

4.2 Roland & Morris Disability Questionnaire scores

The present study did not reveal any statistically significant time effects or group differences at any point in RMDQ scores. Most participants did not report back pain at baseline (79%) or during the trial (72% at t2, 76% at t3), resulting in median values of 0 for all respective time points and change rates. The low prevalence of back pain might be responsible for the absence of effects, however 21% did initially suffer from back pain without showing significant improvements.

The literature on the influence of a combined vitamin D and PRT intervention on back pain is limited, maybe even non-existent, since no trials with this kind of intervention could have be retrieved by searching the internet and the online database of the University of Vienna. In general, there is tentative evidence of PRT and vitamin D supplementation to be eligible methods to reduce back pain among older persons. Alleviation of disability induced by back pain in response to PRT was reported by several meta-analyses (Owen et al., 2020; Searle et al., 2015; Steele et al., 2015; Tataryn et al., 2021). Tataryn et al. (2021) observed better results of PRT interventions with a duration between 12 and 16 weeks, compared to shorter training periods (6 – 8 weeks) in this context, yet the review focussed on posterior-chain PRT. The implementation of exercises strengthening the back muscles specifically might be another possible measure to achieve favourable effects on back pain. These exercises achieved promising results in another trial, even without additional resistances (Hicks et al., 2013). The trial included a big study sample of older subjects (n = 392) and showed reduced back pain (RMDQ) as well as better functional performance after conducting strength training twice a week, although the intervention period was substantially longer (1 year). An intervention of prolonged duration and including exercises focussing on the posterior-chain specifically seem to achieve the best results to improve back pain related symptoms among elderly individuals.

Vitamin D_3 supplementation was also proven effective to alleviate disability related to back pain by previous trials (Akhtar et al., 2020; Brady et al., 2019; Ghai et al., 2017). All of these four trials differ from the present study in their outcome measures, but still show good comparability, since they all used questionnaires assessing the perceived functional disability, similar to the RMDQ. They all used fairly higher overall supplementation doses and two showed again a longer intervention period. Apart from the small number of participants initially reporting back pain, these differences might be additional reasons for the lacking results of the present study. The required vitamin D status to alleviate the self-reported disability caused by back pain might be quite similar to the aforementioned levels associated with improvements in the physical HRQoL domain, since the functional scales of the SF-36 correlate strongly with the RMDQ score (Wiesinger et al., 1999).

In the absence of literature on older populations, the aforementioned studies used for comparison all included younger individuals. This highlights the need of future research of high methodological quality among the elderly, since back pain is one of the most prevalent disorders in the older population and inflicts great personal and economic burden worldwide (Hoy, March, et al., 2014).

4.3 Serum 25(OH)D concentrations

In 16 weeks the share of vitamin D sufficient subjects in the total study population increased from 7% to 46% with significant serum 25(OH)D concentrations rises in VDD and VDM, but

not in CON. The increase of vitamin D levels in CON is not surprising and most likely related to natural vitamin D_3 production, since the trial was conducted between February and July (Wacker & Holick, 2013b). Generally, better improvements were observed in the second phase of the trial, since it was four weeks longer and later in spring, providing higher amounts of vitamin D_3 through photoconversion. VDM was the only group to achieve average vitamin D levels above the sufficiency threshold (> 30 ng/ml) in response to the supplementation and showed expectedly the highest median increase in the serum 25(OH)D concentration. Rather unexpected on the other hand was the missing significance of the post-intervention group effect between CON and VDD in this context. Although the VDD supplementation protocol was in accordance with various RDA recommendations (European Food Safety Authority, 2014; German Nutrition Society, 2012; Ross et al., 2011), more than half of the VDD subjects (56%) remained vitamin D insufficient and 15% were still reported as vitamin D deficient (< 20 ng/ml). The VDD supplementation protocol might have lacked the required potency to compensate for the impaired response in the 25(OH)D concentration to the vitamin D_3 intervention related to the rather high basal vitamin D status in the study population (Mazahery & Von Hurst, 2015). Due to the greater increases in VDM, a higher vitamin D_3 dosage would have most likely achieved elevated vitamin D levels in VDD.

As mentioned before, a higher vitamin D status might have been required in both intervention groups to additionally improve the physical and mental HRQoL. The probably most effective adaption of the intervention protocol in order to achieve increased vitamin D levels, would might have been the use of a 25(OH)D_3 supplement without even increasing the total amount of vitamin D. The same daily dose of vitamin D as in VDD (800IU/day) was administered in the 16-week trial of Bischoff-Ferrari et al. (2012), which included 20 postmenopausal women evenly allocated into two groups. One cohort was provided with a vitamin D_3 supplement, while the other one received the equivalent amount in the form of 25(OH)D_3 (20 µg). Compared to the vitamin D_3 intervention, which left 50% of the subjects below the sufficiency threshold, the 25(OH)D_3 supplementation resulted in a more than twofold serum 25(OH)D concentration and all 10 women were reported vitamin D sufficient post-intervention. These findings prove the higher potency of 25(OH)D_3 over vitamin D_3 to raise serum 25(OH)D concentrations. This was also observed in a shorter intervention trial (Vaes et al., 2018) and in a study, which investigated the efficacy of a smaller 25(OH)D_3 dose in comparison to a higher amount of vitamin D_3 (Cashman et al., 2012).

The use of a greater daily vitamin D_3 dosage remains another practical adaptation of the supplementation protocol, which might have achieved a higher average serum 25(OH)D concentration in the present study. A more frequent mode of administration is associated with slightly faster increases in the vitamin D levels compared to prolonged intervals in between the supplement intakes (Mazahery & Von Hurst, 2015), which seems preferable for

a relatively short trial. The selection of an adequate overall dose appears quite challenging, since the supplementation response is influenced by various factors (Mazahery & Von Hurst, 2015). Looking at another 16-week trial (Gepner et al., 2012) for reference, its daily supplementation dose of 2500 IU of vitamin D_3 might have also been eligible for the present study population. The trial of Gepner et al. (2012) included resembling subjects, who were slightly younger Austrian adults and showed a similar average BMI, but higher basal vitamin D levels. The intervention resulted in an average serum 25(OH)D concentration comparable to those of the aforementioned vitamin D intervention studies, which achieved substantial improvements in the physical and mental self-reported HRQoL (Costan et al., 2014; Yilmaz et al., 2016). Using a lower daily dose would have most likely not resulted in this desired target level, since two 24-month studies (Chen et al., 2014; Tomson et al., 2017), which supplemented 2000 IU of vitamin D_3 per day, reported a similar post-intervention status to that observed in VDM. Therefore, these trials also provide evidence, that increasing the total amount of vitamin D_3 by prolonging the intervention period of the present study might still have resulted in similar median serum 25(OH)D concentrations, since they tend to plateau in response to supplementation after three to six months (Mazahery & Von Hurst, 2015). Plateauing vitamin D levels were observed in several intervention trials with varying dosages (Pekkarinen & Matti, 2016; Ramly et al., 2014; Wood et al., 2012).

The administration of a larger overall vitamin D_3 amount in form of a single high-dose, might have achieved serum 25(OH)D concentrations similar to those observed along with significant increases in HRQoL (Costan et al., 2014; Yilmaz et al., 2016), but most likely with a delay and only for a short period of time. Elderly subjects achieved a vitamin D status comparable to the results of Costan et al. (2014) and Yilmaz et al. (2016) one month after the intake of a single dose of 500000 IU of vitamin D_3 (Sanders et al., 2011). However, after two additional months their vitamin D levels had already dropped by approximately 25% to short above the sufficiency threshold. Using the same amount of vitamin D_3 in a single bolus would have quite likely not achieved greater median increases in the recent study, since a single high-dose usually causes a flatter slope in the serum 25(OH)D concentration response compared to a more frequent administration (Mazahery & Von Hurst, 2015), as mentioned before. This proposition is supported by the findings of two trials (Stricker et al., 2012; Witham, Dove, et al., 2010), which both used a 11.4% higher dosed single bolus (100000 IU) of vitamin D_3 than the overall amount in VDD and still reported similar average serum 25(OH)D concentrations after 16 weeks. The same amount as in VDM, administered as a single high-dose supplement, even resulted in a vitamin D status under the sufficiency threshold in an elderly study population with comparable basal vitamin D levels (Pekkarinen & Matti, 2016).

4.4 Limitations

There are some limitations of this thesis worth mentioning.

As mentioned before, the inefficacy of both vitamin D_3 interventions to create serum 25(OH)D concentrations similar to those observed in tandem with improvements in mental and physical function (Costan et al., 2014; Yilmaz et al., 2016), might be the major limitation of this study, along with the rather short PRT period. Further, the time spent outside by the participants was not monitored. Since the study was conducted between February and July, an additional supply with vitamin D_3 through natural photoconversion might have been expected, given that the subjects were healthy, mobile and community dwelling. The good health status and the low prevalence of LBP among the study population might have reduced the capacity to detect beneficial effects in response to the interventions. Consequently, the reported findings should be transferred with caution to diseased populations. This also applies to the transfer of the results to female subjects, since women were underrepresented in the present study.

5 Conclusion

An isolated beneficial effect of the higher-dose vitamin D_3 protocol on the SF-36 mental component score and sub-domain mental health was observed from baseline to post-intervention. The other HRQoL scores and the perceived disability created by LBP did not respond to the vitamin D_3 and progressive resistance training intervention respectively. Further, no combined influences were detected and the vitamin D_3 supplementation did not enhance the efficacy of the progressive resistance training to improve self-reported HRQoL or the perceived disability related to LBP. Subsequently the present investigation does not promote the additional administration of the vitamin D_3 dosages 800 IU/day and 50000 IU/month to a progressive resistance training intervention for this purpose among healthy elderly adults, who show elevated basal serum 25(OH)D concentrations and HRQoL scores. However, the adaption of the intervention protocols based on the baseline characteristics of a respective study population might still create favourable results in this context. For the subjects of the present study a prolonged exercise intervention as well as a more potent vitamin D supplement could have led to additional detectable results, while the present intervention regimes might be effective among individuals with a lower mental and physical health status.

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