LEHO RIPS

The influence of vitamin D on
the physical performance of conscripts in
the Estonian Defence Forces

DISSERTATIONES MEDICINAE UNIVERSITATIS TARTUENSIS

367

LEHO RIPS

The influence of vitamin D on the physical performance of conscripts in the Estonian Defence Forces

UNIVERSITY OF TARTU
Press

1632

Department of Sports Medicine and Rehabilitation, University of Tartu, Estonia
Centre of War and Disaster Medicine, Estonian Military Academy, Estonia

This dissertation is accepted for the commencement of the degree of Doctor of Philosophy in Medicine on 30th of August 2024 by the Council of the Faculty of Medicine, University of Tartu, Estonia

Supervisors: Madis Rahu, MD, PhD
                    Institute of Clinical Medicine
                    Department of Sports Medicine and Rehabilitation
                    University of Tartu, Estonia

                    Professor Jüri-Toomas Kartus, MD, PhD
                    Department of Orthopaedics
                    Institute of Clinical Science
                    Sahlgrenska Academy, University of Gothenburg, Sweden

                    Alar Toom, MD, PhD
                    Department of Orthopaedics
                    Central Finland Central Hospital, Finland

                    Mart Kull, MD, PhD
                    Viljandi Hospital, Estonia

Reviewers: Associate professor Katre Maasalu, MD, PhD
                    Institute of Clinical Medicine
                    Department of Orthopaedics
                    University of Tartu, Estonia

                    Professor Priit Kaasik, PhD
                    Institute of Sport Sciences and Physiotherapy
                    Department of Exercise Biology
                    University of Tartu, Estonia

Opponent: Professor Adad Baranto, MD, PhD
                    Department of Orthopaedics
                    Institute of Clinical Science
                    Sahlgrenska Academy, University of Gothenburg, Sweden

Commencement: December 6th 2024"

"The roots of education are bitter, but the fruit is sweet."
— *Aristotle*

"What is the fastest? The mind. It travels through everything."
— *Thales*

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I Rips, L., Toom, A., Kuik, R., Varblane, A., Mölder, H., Kull, M., Kartus, J.-T., Gapeyeva, H., & Rahu, M. (2023). **Severe deficiency of vitamin D has no negative effect on physical performance during military training.** *The Journal of Sports Medicine and Physical Fitness, 63*(2), 329–338. https://doi.org/10.23736/S0022-4707.22.14123-X

II Rips, L., Toom, A., Kuik, R., Varblane, A., Mölder, H., Tammaru, M., Kull, M., Ööpik, V., Kartus, J.-T., Gapeyeva, H., & Rahu, M. (2022). **Seven-month wintertime supplementation of 1200 IU vitamin D has no effect on hand grip strength in young, physically active males: A randomized, controlled study.** *Journal of the International Society of Sports Nutrition, 19*(1), 437–454. https://doi.org/10.1080/15502783.2022.2100718

III Rips, L., Toom, A., Kuik, R., Varblane, A., Mölder, H., Kibur, R., Laidvere, M., Kull, M., Kartus, J.-T., Gapeyeva, H., & Rahu, M. (2024). **High dose vitamin D supplementation decreases the risk of deficiency in male conscripts, but has no effect on physical performance – a randomized study.** *Journal of Experimental Orthopaedics,* e12023. https://doi.org/10.1002/jeo2.12023.

Author's contribution
I The author was responsible for the study design, took part in all stages of the study, and was the main person responsible for writing the paper.
II The author was responsible for the study design, took part in all stages of the study, and was the main person responsible for writing the paper.
III The author was responsible for the study design, took part in all stages of the study, and was the main person responsible for writing the paper.

Additional relevant papers by the author not included in this thesis:

I Rips, L., Rahu, M., Kuik, R., Varblane, A., Olveti, I., Ööpik, V., Mölder, H., Timpmann, S., Tammaru, M., Toom, A., Kartus. J.-T., & Gapeyeva, H. (2020). **Self-reported knee pain does not impact physical training negatively in conscripts.** *Military Medicine, 14*(7–8), 1134–9. https://doi.org/10. 1093/milmed/usz486.

II Ööpik, V., Timpmann, S., Rips, L., Olveti, I., Kõiv, K., Mooses, M., Mölder, H., Varblane, A., Lille, H.-R., & Gapeyeva, H. (2017) **Anabolic adaptations occur in conscripts during basic military training despite high prevalence of vitamin D deficiency and decrease in iron status.** *Military Medicine, 182*(3), 1810–8. https://doi.org/10.7205/MILMED-D-16-00113.

ABBREVATIONS

APFT	Army Physical Fitness Test
B	Baseline (Study III)
BL	Baseline
BMI	Body Mass Index
BW	Between
Ca	Calcium
cm	Centimetre
EFSA	European Food Safety Authority
ES	Endocrine Society
FP	Follow-up
FUI	Follow-up I (Study III)
FUII	Follow-up II (Study III)
FUIII	Follow-up III (Study III)
i-Ca	Ionized calcium
IU	International unit
kg	Kilogram
n.s.	Non-significant
PTH	Parathyroid hormone
RDA	Recommended Dietary Allowance
SD	Standard deviation
UK	United Kingdom
UL	Upper limit
US	United States
UVB	Ultraviolet B irradiation
WHO	World Health Organization
WI	Within
1.25(OH)D	1.25-hydroxyvitamin D
25(OH)D	25-hydroxyvitamin D

1. INTRODUCTION

There has been a growing interest worldwide in vitamin D deficiency and its consequences to human health and physical performance during the last decades (Knapik et al., 2021; Menon et al., 2020; Wintermeyer et al., 2016). It is well known that long-lasting vitamin D deficiency has many negative consequences to human body function (Holick et al., 2011). Vitamin D has key roles in musculoskeletal health, especially in bone metabolism, and deficiency could increase the risk of osteopenia and osteoporosis, muscle weakness, risk of fracture, disorders of the immune system, and mental health problems (Carswell et al., 2018; Halliday et al., 2011; Holick, 2003; Holick et al., 1995, 2011; Sinha et al., 2013). Problems related to vitamin D deficiency can occur in all age groups of the general population, as well as in individuals participating in high-demand activities, including military service (Gaffney-Stomberg et al., 2022; Harrison et al., 2021; Sivakumar et al., 2019). However, the role of vitamin D for physical performance and muscle strength, and its relation to high-demand physical effort is more controversial (Carswell et al., 2018; Geiker et al., 2017; Heileson et al., 2022; Mason et al., 2019; Menon et al., 2020; Stockton et al., 2011; Zhang et al., 2019). There are only a few studies showing a positive effect of supplementation or that a higher level of blood serum vitamin D results in better physical performance (Carswell et al., 2018; Stockton et al., 2011; Zeitler et al., 2018).

Vitamin D is a unique fat-soluble hormone-like vitamin with an extremely wide range of biological actions in the human body (Giustina et al., 2020). Vitamin D receptors are found in almost all human cells, including muscle cells (Girgis et al., 2013; Montenegro et al., 2019; Wang et al., 2012).

Ultraviolet (UVB) irradiation is the main source of natural synthesis of vitamin D in the human body (de Gruijl, 2011). Fat-rich food, such as fish, egg, and meat, are natural sources of vitamin D3, and mushrooms are a natural source of vitamin D2 (Lamberg-Allardt, 2006). Food fortification (Jääskeläinen et al., 2017; Spiro & Buttriss, 2014) and supplementation are other methods to increase vitamin D levels in the human body.

Vitamin D is inactive in the human body and needs a two-step hydroxylation from 25(OH)D to the active form 1,25(OH)D (DeLuca, 2004). The main form, which is also the indicator of vitamin D status in human blood serum, is the more stable 25(OH)D (Calvo et al., 2005).

There is still a debate surrounding normative upper levels of vitamin D. According to the Endocrine Society (ES), > 75 nmol/l should be the target level of blood serum 25(OH)D (Holick et al., 2011). The recommended target level according to the European Food Safety Authority (EFSA) and the US Institute of Medicine is > 50 nmol/l in all age groups (Dietary Reference Values for Vitamin D EFSA, 2016; Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium, 2011). Some studies even suggest normative levels of 75–125 nmol/l (Płudowski et al., 2013).

In military service, high physical and mental stress are faced during training and preparation periods. Specific conditions, such as geographic region, special clothing, skin camouflage, training conditions, weather and environmental conditions (e.g. shelters, submarines), and high physical stress, could put soldiers at higher risk of vitamin D deficiency (Fagnant et al., 2022; Henriques et al., 2022; McCarthy et al., 2019; Sivakumar et al., 2019).

Physical condition is crucial in the army, especially in life-threatening situations. To test the training effect on physical performance, the Army Physical Fitness Test is widely used in the US Army (Army Basic Training PFT Military.com) and has also been adapted by the Estonian Army. The hand grip strength test is another simple and reliable test of physical fitness (Granlund et al., 2018).

Based on current, limited evidence, vitamin D deficiency is very common among the Estonian population (Kull et al., 2009). In military service, young males are put under higher physical stress than in everyday life; therefore, a higher risk of vitamin D deficiency might occur during military training.

Considering this, three studies were performed on young male Estonian conscripts to measure the effect of vitamin D supplementation, varying from placebo to 4000 IU daily, on blood serum 25(OH)D values and physical fitness during military service.

2. LITERATURE REVIEW

2.1 Vitamin D

2.1.1 Vitamin D history

Vitamin D was first introduced one hundred years ago by McCollum as an anti-rachitic substance called vitamin A (McCollum et al., 1922). Some years later, Adolf Windaus determined the chemical structure of vitamin D3, resulting in the Nobel Prize in 1928 (Windaus & Grudmann, 1936). Since then, food fortification and supplementation with different forms of vitamin D have become widespread and have led to the reduction of Ricket's disease and osteomalacia in many countries.

2.1.2 Vitamin D characterization

Vitamin D comprises a group of over 50 chemically related metabolites (Alonso et al., 2023; Jenkinson et al., 2021). These metabolites are fat-soluble secosteroids and due to their lipophilic nature, they circulate bound to vitamin D binding protein, albumin, and lipoproteins (Herrmann, 2023). The two main forms, the skin-derived animal form vitamin D3 (cholecalciferol) and the plant-based vitamin D2 (ergocalciferol), are mainly used for vitamin D description (Cardwell et al., 2018; Jäpelt & Jakobsen, 2013; Lips, 2006). Vitamin D metabolites have an extremely wide range of biological actions in the human body. They are mostly known for their important role in calcium and bone metabolism (Lips, 2006). Vitamin D receptors are found in almost all human body cells (Wang et al., 2012), including muscle cells (Montenegro et al., 2019).

2.1.3 Vitamin D sources and factors affecting absorption

Ultraviolet (UVB) irradiation is the main source of natural synthesis of the animal form vitamin D3 in the human body (de Gruijl, 2011; Holick, 2004) and the plant form vitamin D2 in fungi and yeast (Cardwell et al., 2018). Provitamin D3 (7-dehydrocholesterol) is produced by UVB-exposure of naked skin in many animals, including humans. In humans, 90% of vitamin D is formed in the skin tissue under direct sunlight. UVB irradiation converts provitamin D (7-dehydrocholesterol) to previtamin D3 and finally to vitamin D3 in the human body (Aydın et al., 2019; Holick et al., 1995; Holick, 2003; C. Lamberg-Allardt, 2006) (Figure 1.). Skin pigmentation, clothing covering the skin, regular use of topical sunscreens, working indoors, ageing, lower zenith angle of the sun, and specific conditions, for example in military situations, such as skin camouflage, training conditions, weather, submarines, and shelters, could put persons at risk of decreased production of vitamin D3 (Armstrong et al., 2020; Gaffney-Stomberg et al., 2019; Henriques et al., 2022; Sivakumar et al., 2019).

Vitamin-D3-rich sources include animal-based food products like fatty fish (salmon, sardines, mackerel), fish oil, eggs, liver, meat, dairy products, offal, and poultry (Holick, 2004; Lamberg-Allardt, 2006). Only 10–20% of total vitamin D

is food-derived under normal physiologic circumstances (Holick, 2011). Modified food consumption (vegan) and lack of dairy products in a daily menu likely decreases animal-based vitamin D intake (Fagnant et al., 2022).

Vitamin D2 is found in fungi and yeast, and can be found in plant-based products as a result of contamination with fungi (Cardwell et al., 2018; Lamberg-Allardt, 2006). According to the study of Jäpelt&Jakobsen, vitamin D is also found in potato, tomato, and pepper (Jäpelt & Jakobsen, 2013). Still, the amounts obtained as plant-based vitamin D are very limited and probably do not increase vitamin D levels considerably.

Food fortification with vitamin D is common in some countries, including in Scandinavia (Jääskeläinen et al., 2017; Lamberg-Allardt et al., 2013) and North America (Calvo & Whiting, 2013). Vitamin D is added mainly to dairy products – milk, cheese, and yogurt. Based on Scandinavian studies, food fortification decreases vitamin D deficiency, but daily food consumption behaviour could affect vitamin D levels more; for example, decreased consumption of milk products could affect this.

Supplementation is another source of vitamin D. Different products are available on the market, including oil, oil capsules, oil spray, tablets etc. Skipping winter and springtime supplementation raises the risk of vitamin D deficiency, especially in the Nordic countries.

In the case of extreme deficiency of vitamin D, pharmacological products with extreme amounts of cholecalciferol (vitamin D3) are available for injection.

There are also other general risk factors resulting from decreased bioavailability of vitamin D, such as adiposity, liver failure, senectitude, darker skin tone, smoking, and genetic predispositions. There are also individual variations, and in some circumstances gender differences, with a higher risk related to deficits in females (Wiciński et al., 2019).

2.1.4 Vitamin D blood serum measurements and metabolism

Vitamin D3 and D2 are metabolized by the same enzymes and from similar metabolites. For the measurement of vitamin D metabolites, a direct chemiluminescent immunoassay method is used (Herrmann, 2023).

Vitamin D is inactive in the human body. A two-step hydroxylation is needed to produce the biologically active form of vitamin D: firstly in the liver to form 25(OH)D with the contribution of CYP2R1 (25-hydroxylase), and secondly in the kidneys, where CYP27B1 (1alfa-hydroxylase) synthesizes the biologically active form, 1,25(OH)D (Herrmann, 2023; Wrzosek et al., 2020) (Figure 1.). 25(OH)D is the main vitamin D metabolite used to determine vitamin D status in humans. The main reason for this is the longer blood serum half-life of 25(OH)D of up to 2–3 weeks. The biologically active form of vitamin D, 1,25(OH)D, has a shorter half-life of only 4–6 hours, and circulating levels of this in blood serum are a thousand-fold less than that of 25(OH)D. This makes measurement of vitamin D status with 1,25(OH)D more complicated, and therefore, this is not routinely used (Alonso et al., 2023; Holick, 2009).
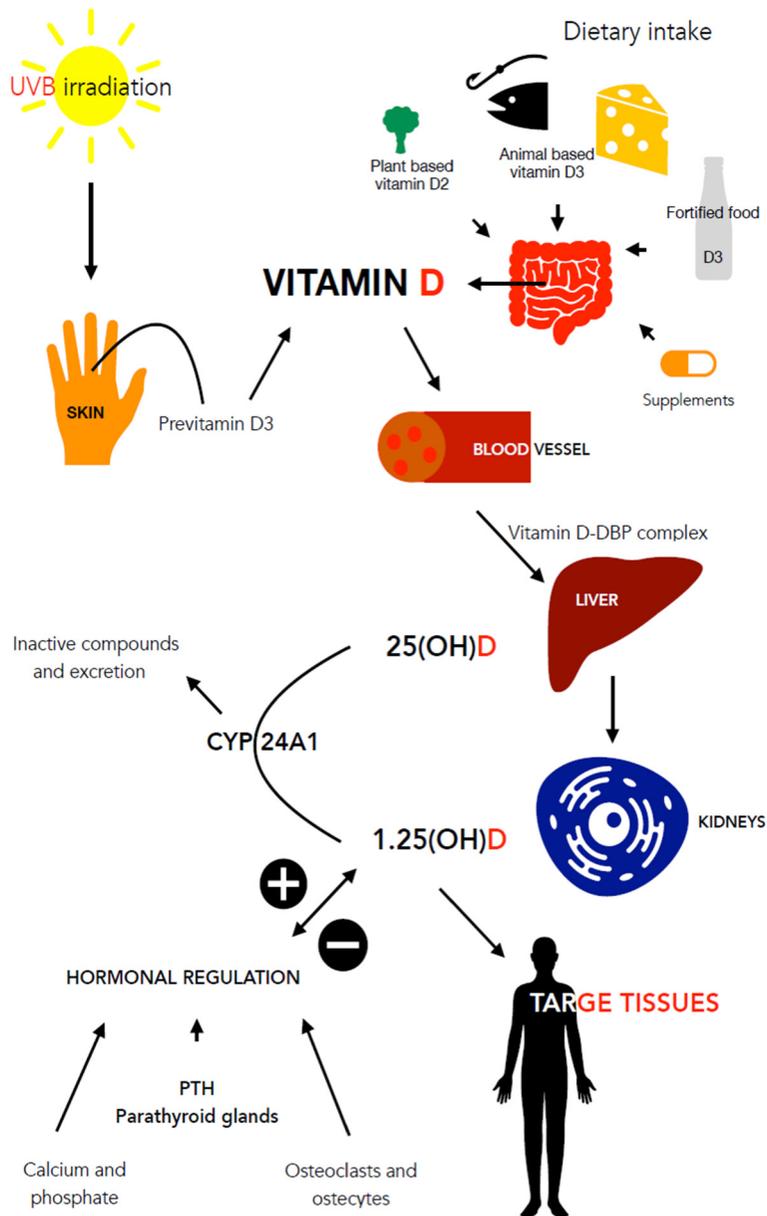
Figure 1. Vitamin D synthesis and metabolism. Simplified schematic of vitamin D sources and metabolism in the human body. The main natural vitamin D sources in the human body are UVB irradiation and fat-rich food (fish etc.). Different supplements are the main artificial sources of vitamin D. 25(OH)D is the main form used for the measurement of vitamin D serum levels. 1.25(OH)D is the active form of vitamin D in the human body and has a direct relation with the hormonal regulation of the parathyroid gland and target tissues.

2.1.5 Vitamin D 25(OH)D blood serum normative values

There is still some debate over what normative values of vitamin D blood serum 25(OH)D levels are: > 50 nmol/l or > 75 nmol/l. According to the Endocrine Society, blood serum 25(OH)D values for deficiency are defined as < 20 ng/ml or < 50 nmol/l, and sufficiency is defined as > 30 ng/ml or > 75 nmol/l, which is required to increase bone mineralization and muscle metabolism (Holick et al., 2011). On the other hand, Nordic Nutrition Recommendations recommends 50 nmol/l as a sufficient target value of blood serum 25(OH)D in adults (Lamberg-Allardt et al., 2013). The US Institute of Medicine (IOM) report from 2011 (Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium, 2011) supports the Nordic Nutrition Recommendations, and it states that deficiency is < 30 nmol/l, 30–50 nmol/l is inadequate, and > 50 nmol/l is a sufficient blood serum 25(OH)D concentration. The European Food Safety Authority (EFSA), in their 2016 consensus, claimed that 50 nmol/l is a suitable target value for all age and gender groups (Dietary Reference Values for Vitamin D EFSA, 2016). Controversially, Bischoff-Ferrari et al. (2006) stated that the blood serum concentration of 25(OH)D should not be below 75 nmol/l, with 90–100 nmol/l being the optimum target; this is also supported by Płudowski et al. (2023), who suggested increasing the target range of 25(OH)D levels up to 75–125 nmol/l. There is more consensus over deficiency levels; blood serum 25(OH)D values under < 25 nmol/l tend to be considered a deficiency (Wahl et al., 2012) or severe deficiency (Allison et al., 2015) (Figure 2.).

🟩	75 + nmol/l	Sufficient
🟧	50-74.9 nmol/l	Insufficient
🟨	25-49.9 nmol/l	Deficiency
🟥	0-24.9 nmol/l	Severe deficiency

Figure 2. Colour-coded blood serum vitamin D 25(OH)D cut-off values used in all three studies included in the thesis.

2.1.6 Vitamin D status in Estonia and Nordic countries

There are limited studies based on the Estonian population and none on younger healthy males related to the vitamin D status. A population-based study in Estonia focusing on 15-year-olds found the mean blood serum 25(OH)D concentration to be 43.7 nmol/l during winter and 59.3 nmol/l during summer. The authors concluded that vitamin D deficiency is highly prevalent throughout the year among the Estonian population. One of the risk factors in this case is living in a region with a lack of sun exposure at a latitude of 59°N (Kull et al., 2009). Another multicenter European study, also involving the Estonian population, included 2171 3- to 15-year-old children, found vitamin D deficiency in 63% of cases, with blood serum 25(OH)D values < 50 nmol/l (Wolters et al., 2022). Finnish-population-based studies have also found vitamin D deficiencies in all age groups during the winter season (Jääskeläinen et al., 2017; Laaksi et al., 2006; Lamberg-Allardt et al., 2001). Similar seasonal variations in vitamin D levels, with a high level of vitamin D deficiency during winter, have also been reported in other European studies (Lips et al., 2006, 2019; Spiro & Buttriss, 2014).

2.1.7 Vitamin D supplementation

To decrease the risk of vitamin D deficiency, regular supplementation is common practice worldwide. The appropriate amount of supplementation is still under debate, and there is lack of consensus on this. The European Food Safety Authority (EFSA) panel's suggestion for adults is daily intake of 15 µg (600 IU) in order to reach a range between 34 nmol/l and 91 nmol/l (Dietary Reference Values for Vitamin D EFSA, 2016). The same daily intake of 600 IU is suggested by the Nordic Nutrition Recommendations panel (Lamberg-Allardt et al., 2013). The Endocrine Society committee suggests a daily supplementation between 1500 and 2000 IU for those in the population at risk of deficiency, and they suggest an upper limit of 4000 IU in young men (Holick et al., 2011). In line with this, recent Polish guidelines suggest a tolerable daily upper intake of up to 4000 IU in adults aged 19 years and above (Płudowski et al., 2023). In Estonia, the suggested safe daily supplementation with vitamin D was 1200 IU/day in 2015, and this was raised to 4000 IU/day in 2019 (Table 1).

Table 1. Vitamin D daily intake and supplementation recommendations. RDA includes food intake, fortified food, and supplements.

Age group	EFSA panel (2016) RDA/UL	Endocrine Society (2011) RDA/UL	Nordic Nutrition Recommendations (2013) RDA/UL	Preventing and treating vitamin D Polish update (2023) RDA/UL	Estonian Food Safety Agency UL
Children 1–17 years	600 IU				
Children 1–8 years		600 IU/2500–3500 IU			
Children 1–10 years				600 IU/2000 IU	
Children 11–18				1000–2000 IU/4000 IU	
Adults > 18 years	600 IU		600 IU		4000 IU
Adults > 19 years				1000–2000 IU/4000 IU	
Males and females 9–70 years		600 IU/4000 IU			
Adults > 19 obesity				UL 10000 IU	

Abbreviations: EFSA – European Food Safety Authority; RDA – recommended dietary allowance; UL– upper limit; IU – international unit.

2.1.8 Vitamin D supplementation side effects and risk factors

It is known that excessively high supplementation doses of Vitamin D or very high blood serum levels of 25(OH)D together with low calcium intake can increase the calcium blood serum levels outside the normal range, causing increase in bone resorption and decrease in bone mineralization (Carmeliet et al. 2015). There is also a risk of hypercalcemia causing general gastrointestinal problems such as constipation and hypercalciuria with renal calculi. Still based on current evidence, a blood serum 25(OH)D level of 250 nmol/l is a safe upper limit and the threshold of toxic levels is more than 750 nmol/l (Glenville 2008).

2.1.9 Vitamin D in relation to physical fitness

Due to the importance of demanding physical efforts among professional sportsmen and women and military personnel, there has been a growing interest in the role of vitamin D on physical fitness and general health in recent decades (Aydın et al., 2019; Carswell et al., 2018; Cashman et al., 2011; Fagnant et al., 2022; Fogleman et al., 2022; Gaffney-Stomberg et al., 2019; Geiker et al., 2017; Halliday et al., 2011; Henriques et al., 2022; Laaksi et al., 2006; Mielgo-Ayuso et al., 2018; Ööpik et al., 2017; Savolainen et al., 2021; Schaad et al., 2019; Scott et al., 2019; Sivakumar et al., 2019; Wiciński et al., 2019; Willis et al., 2008; Wintermeyer et al., 2016). High-level physical fitness and general good health play a crucial role in potentially life-threatening situations encountered in military service and could also affect maximum effort in professional sports. Vitamin D deficiency is not a rare condition and is commonly diagnosed in army recruits (Armstrong et al., 2020; Fagnant et al., 2022; Knapik et al., 2021; Laaksi et al., 2007) and in professional athletes (Wiciński et al., 2019). A prospective cohort study in the UK Army reported that vitamin D is clearly associated with endurance performance; however, it showed that power and strength are not affected by vitamin D (Carswell et al., 2018). This is supported by the study of Heileson et al. (2022), in which a correlation between physical fitness and vitamin D deficiency was found. Similar findings showing a positive correlation of vitamin D with physical performance have been found among judoists (Książek et al., 2018) and professional soccer players (Koundourakis et al., 2014). There is also evidence suggesting that muscle energy metabolism and regular physical activity have an important role in maintaining adequate vitamin D levels (Mason et al., 2019). Conversely, Menon et al. (2020) found that vitamin D supplementation did not improve muscle strength or cardiorespiratory endurance in military recruits. No enhancement of muscle recovery was found during two months of 3000 IU supplementation in male rowers (Mielgo-Ayuso et al., 2018). Furthermore, many studies show no effect of vitamin D supplementation or any correlation between vitamin D levels and physical performance: in soccer players (Skalska et al., 2019), ice hockey players (Orysiak et al., 2018), in a strength training group (Savolainen et al., 2021), in the sprint performance of professional rugby players (Fairbairn et al., 2018), or in Gaelic footballers (Todd et al., 2017).

Current evidence is insufficient; there is lack of knowledge and conflicting results on how vitamin D deficiency or vitamin D status and supplementation affect physical performance in a young, healthy, physically active population.

2.2 Blood serum markers related to vitamin D

2.2.1 Parathyroid hormone

Parathyroid hormone (PTH) is produced by four parathyroid glands, and it is responsible for maintaining blood serum calcium homeostasis. Normal blood serum values range between 1.48 and 7.83 pmol/l. Blood serum calcium and PTH levels are inversely correlated. When blood serum calcium levels are low, PTH levels increase and, together with vitamin D, it starts to mobilize calcium stores and increase calcium absorption and reabsorption. In the reverse situation, where there is an increase in blood serum vitamin D and calcium levels, they bind to parathyroid gland receptors and inhibit PTH production (Lofrese et al., 2024). Seasonal variation of PTH was described in a large cohort study by Shen et al. (2020). Fluctuations of PTH levels are also related to diet, time of day, renal function, and physical activity, but the most important suppressor of PTH levels is optimal serum levels of 25(OH)D (Bischoff-Ferrari et al., 2006).

2.2.2 Calcium and ionized calcium

Many biochemical processes in the human body involve calcium. Calcium is the fifth most common element and the most prevalent cation in the human body and approximately 90% of calcium is in the skeleton. Calcium has a crucial role in proper cardiac function, bone metabolism and structural integrity, muscular contractions, and enzymatic signal actions. PTH regulates blood serum calcium levels. Normal blood serum values range between 2.15 and 2.6 mmol/l. In the blood serum, 50% of calcium is free calcium – ionized calcium. Ionized calcium is the biologically active form of calcium, with normal blood serum values ranging between 1.12 and 1.32 mmol/l. Extracellular calcium provides calcium ions for maintaining intracellular calcium, bone mineralization, blood coagulation, and plasma membrane potential. Furthermore, calcium has a crucial role in muscle contraction (Drake & Gupta, 2024).

2.2.3 Testosterone and cortisol

Testosterone and cortisol have crucial roles in muscle fitness, physical performance, and general health (Casto et al., 2016). Normative blood serum values of testosterone range between 8.4 and 28.7 nmol/l in males, and cortisol values range between 138 and 690 nmol/l. Vitamin D is linked to testosterone production in the human body, and supplementation of vitamin D has shown a positive effect on testosterone levels (Chen et al., 2019; Nimptsch et al., 2012). It is also known

that increased levels of testosterone can improve physical performance (Handelsman et al., 2018; Mielgo-Ayuso et al., 2018). Cortisol, commonly called the stress hormone, is one of the glucocorticoids, and it has an important role in regulating muscle function, energy homeostasis, metabolism, and adaptation to physical exercises (Kraemer et al., 2020). However, increased levels of cortisol can decrease physical performance ability (Duclos et al., 2003).

2.3 Physical fitness tests

2.3.1 Army Physical Fitness Test (APFT)

The Army Physical Fitness Test (APFT) was designed to test general physical fitness, including muscular strength, endurance, and cardiovascular respiratory ability of Unites States Army soldiers. The test was first introduced in 1980. The test is based on three events: 2 minutes of push-ups, 2 minutes of sit-ups, and a two-mile (3.2 km) run. The push-up test measures the endurance of the chest, shoulder, and triceps muscles. The sit-up test measures the endurance of the abdominal and hip-flexor muscles. The two-mile run measures aerobic fitness and leg muscle endurance. Each event results in 0–100 points and they are gender- and age-adjusted. A minimum of 60 points is needed in each event to pass the test; a minimum overall total of 180 points is therefore needed, so the total scores to pass the test can range from 180 to 300 points. Score tables can be found in the Army FM 7-22 and Department of the Army Form 705, APFT scorecard ('United States Army Physical Fitness Test', 2024). The modified APFT has been widely used to test conscripts and professional soldiers in the Estonian Army for decades as a way to follow conscripts' physical performance capacity during military service, and it is well known by military coaches. The only difference to the original test in the Estonian version is in the running event, where the two-mile distance is calculated in kilometers as a total of 3.2 km.

2.3.2 Hand grip strength test

The hand grip strength test is the most common test used to evaluate grip muscle strength. Isokinetic and hydraulic dynamometers are the most commonly used instruments to assess grip strength (Huerta Ojeda et al., 2021). The hand grip strength test is a reliable indicator of physical function and health status and is used in almost all age groups and for people of all physical levels of activity (Bohannon, 2015; Burdukiewicz et al., 2020; Dodds et al., 2014). Reference values are based on gender, age, and geographical region (Chen et al., 2018; Dodds et al., 2014, 2016). For army recruits, the hand grip strength test is used to test for shooting stability (Christopher et al., 2019) or to test general physical performance (Gonçalves et al., 2018).

2.4 Rationale of the studies

Long-term vitamin D deficiency has well known negative side effects such as osteopenia, osteoporosis, and, in some circumstances, to worsen general health and physical performance in adults. Plenty of sun and outdoor physical activities, as well as balanced food intake, are the best and most well-known methods of maintaining natural vitamin D production in the human body. Still, there is debate concerning normative levels of 25(OH)D and daily intake and supplementation dosages. In many international studies it has been shown that wintertime vitamin D supplementation and food fortification can increase blood serum 25(OH)D levels. Increasing interest in vitamin D on physical performance has been seen during recent decades. Still, controversial outcomes have been found for and against supplementation and vitamin D effects on muscle strength and endurance capability. Despite widely known prevention methods, a surprisingly high number of young Estonian male army conscripts presented with vitamin D deficiency in our pilot studies. More concerning is the high number of conscripts with vitamin D deficiency or severe deficiency during winter and springtime, and these findings motivated us to conduct more thorough investigations. It was found that suggested supplementation dosages in Estonia were based on international studies from geographically different locations where food fortification was often present. Lack of population-based, randomized studies made us interested in performing such studies to examine the vitamin D situation in Estonia. Therefore, three studies were designed to evaluate vitamin D status and its relationship to physical performance. The hypotheses of the studies were as follows: 1) without supplementation or supplementation with low dosages of 600 IU, vitamin D deficiency occurs during wintertime, and supplementation with 1200 IU or with 4000 IU decreases the risk in deficiency, 2) severe deficiency effects physical performance negatively and supplementation increases physical performance.

3. AIMS AND HYPOTHESES

The main aim of the thesis was to evaluate vitamin D seasonal variations with and without vitamin D supplementation using different doses and assess the effect on physical performance in terms of the hand grip strength test and APFT, during military service in Estonian conscripts. The levels of parathyroid hormone (PTH), testosterone, cortisol, calcium, ionized calcium and BMI were evaluated as secondary outcomes of the study.

Study I. The aim of this study was to evaluate blood serum 25(OH)D levels during military service and the effect of deficiency and severe deficiency of vitamin D (25(OH)D) on physical performance during training. The hypothesis of this study was that severe deficiency of vitamin D would affect physical fitness negatively during military training. PTH and Ca blood serum values were evaluated as secondary outcomes.

Study II. The aim of this study was to evaluate the effect of vitamin D supplementation with 1200 IU on blood serum 25(OH)D values and physical performance compared to placebo supplementation. The hypothesis of this study was that without oral vitamin D supplementation, vitamin D (25(OH)D) deficiency occurs during the winter season, and this can cause a decrease in hand grip strength. PTH, Ca, i-Ca, testosterone and cortisol blood serum levels were evaluated as secondary outcomes.

Study III. The aim of this study was to evaluate vitamin D supplementation with 4000 IU or 600 IU in terms of the effect on physical performance and blood serum 25(OH)D values. The hypothesis of this study was that oral vitamin D supplementation with 4000 IU decreases the risk in vitamin D deficiency more than 600 IU during the winter season and increases physical fitness. PTH, Ca and i-Ca blood serum levels and BMI were evaluated as secondary outcomes.

4. MATERIALS AND METHODS

4.1 Materials

4.1.1 Recruitment and informed consent

In all three studies the recruits at the Kuperjanov Battalion, Võru, Estonia (latitude 58°N, which corresponds to southern Alaska and Scotland) were informed of the purpose of the study, recruitment criteria, and follow-up methods Only those who volunteered to participate in the study and signed informed consent after this first briefing were included in the studies.

4.1.2 Participants in Study I (Rips et al., 2023)

All conscripts (n = 410) entering 10-month military service in July 2015 were asked to participate in the first briefing of the study. A total of 98 male conscripts volunteered to participate initially; 10 of them, however, moved to another military unit, and thus, 88 entered the study. Two further conscripts refused to continue the study after the first week. Data from 86 conscripts at baseline and from 65 in March the year after, all of Caucasian origin, were included in the final analysis (Figure 3.).
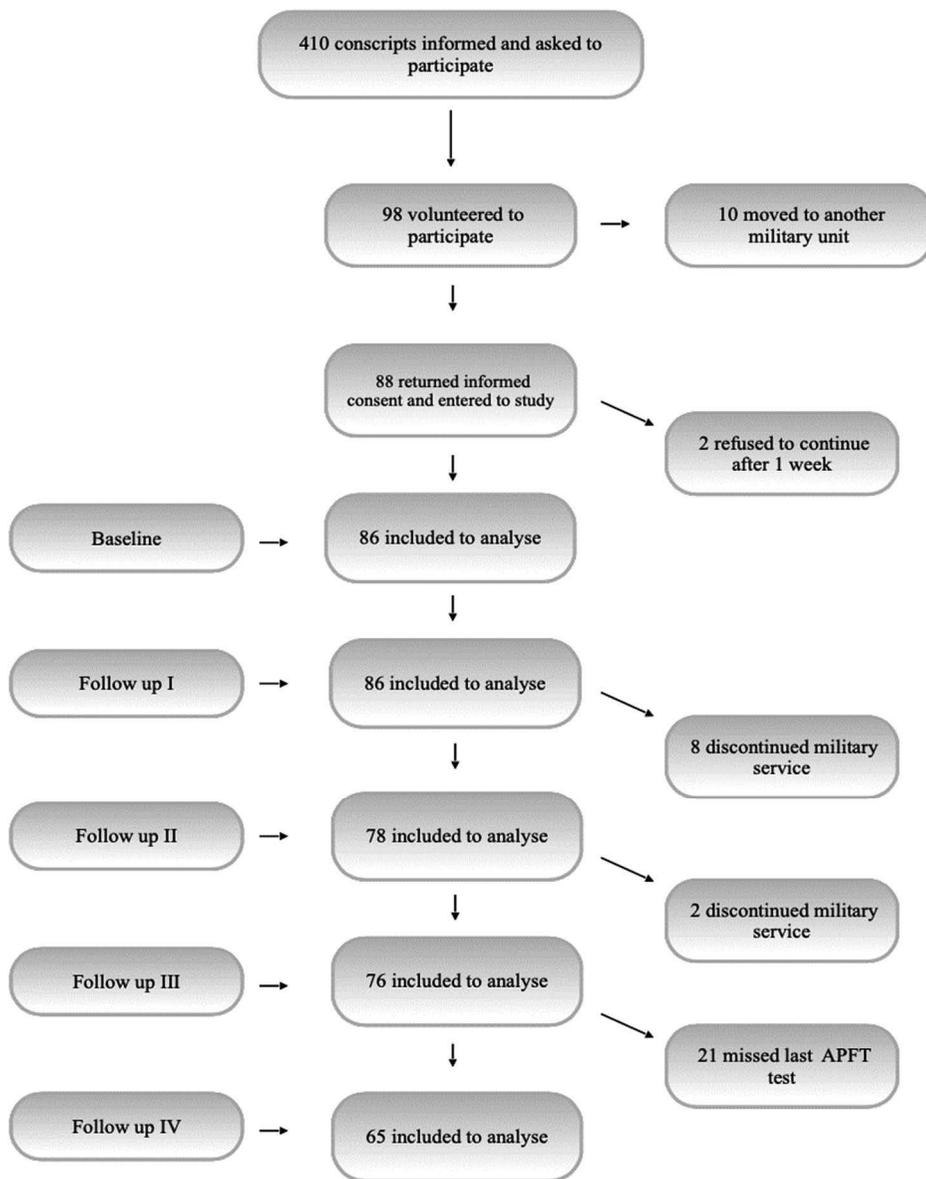
Figure 3. Flow chart describing participation in Study I

4.1.3 Participants in Study II (Rips et al., 2022)

All conscripts (n = 403) entering military service in October 2016 were asked to participate in the first briefing of this study. A total of 65 male conscripts volunteered to participate initially and 63 of them returned their informed consent. Ten conscripts – five in the intervention group and five in the control group – were later excluded from the study due to premature cessation of their military service: two for mental health problems, two for lower-back pain, one for polyarthritis, and five for other medical reasons. Data from 53 conscripts, all of Caucasian origin, were included in the final analysis: 27 in the intervention group with 1200 IU vitamin D substitution and 26 in the control group (Figure 4.).
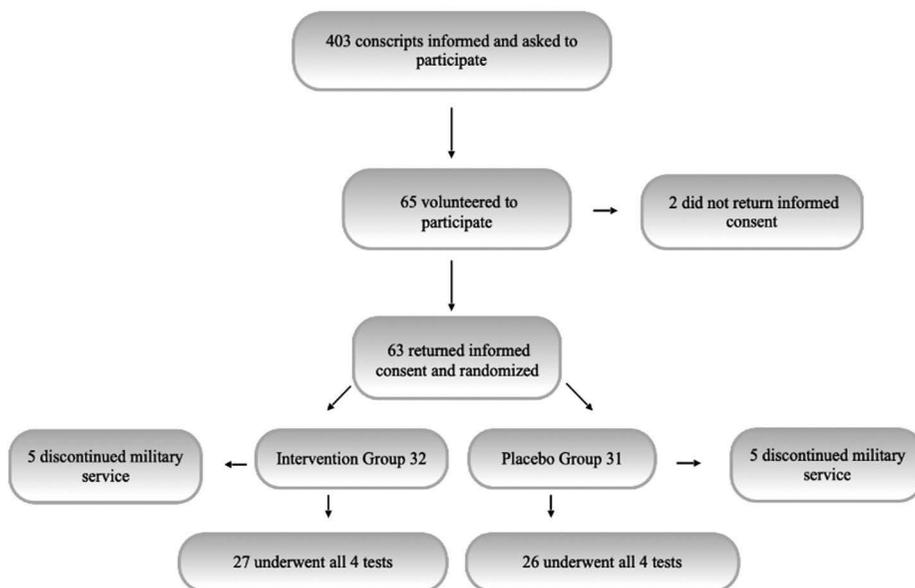
Figure 4. Flow chart describing participation in Study II

4.1.4 Participants in Study III (Rips et al., 2024)

All conscripts (n = 438) entering military service in July 2021 were asked to participate in the first briefing of this study. A total of 135 conscripts initially volunteered to participate, and 116 of them returned their informed consent. Four females were excluded from the study, because it was impossible to standardize their physical test results with male participants. Fourteen conscripts – seven in the 600 IU group and seven in the 4000 IU group, were later excluded from the study due to premature cessation of their military service: five for mental health problems, three for lower-back pain, and six for other medical reasons. Data from 112 conscripts, all of Caucasian origin, were included in the final analysis with 55 conscripts in the 600 IU group and 57 in the 4000 IU group. Home-based

vitamin D supplementation was registered in five conscripts who all were told to discontinue use at baseline (Figure 5.).
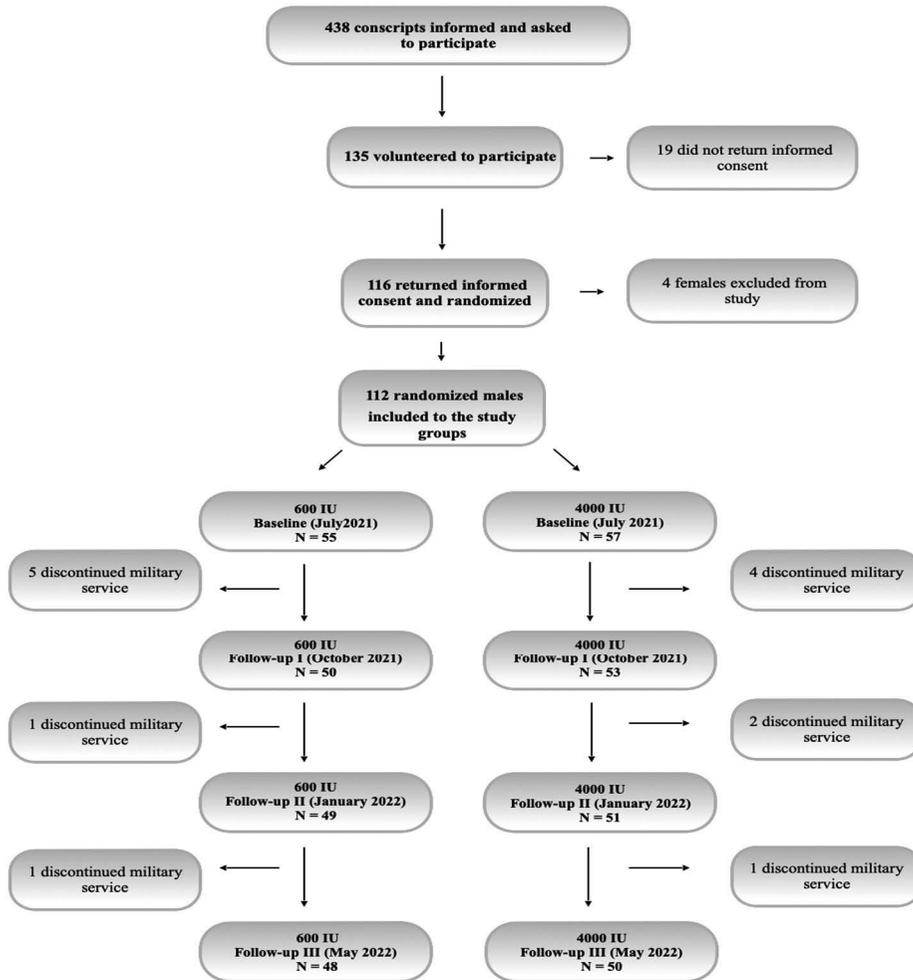
Figure 5. Flow chart describing participation in Study III

4.2 Methods

4.2.1 Randomization

Randomization was used in Study II and Study III.

In Study II, computed randomization was used in a placebo-controlled triple-blinded trial to divide conscripts into two subgroups: either the intervention group, in which conscripts received vitamin D3 olive oil capsules (1200 IU/ 30 µg), or the control group, in which conscripts received placebo olive oil

capsules. Both types of capsules were standardized for size and colour, and they were administered once per day, in the morning before breakfast, for seven months.

In Study III, computed randomization was used to divide conscripts into two subgroups for vitamin D supplementation in a triple-blinded trial. Conscripts in both groups received vitamin D3 oil capsules; in one group the daily dosage was 600 IU/15 µg, and in the other group the daily dosage was 4000 IU/100 µg. Both types of capsules were standardized for size and colour, and they were administered once per day, in the morning before breakfast, for ten months.

4.2.2 Vitamin D supplementation

Vitamin D supplementation was used in Study II and Study III.

In Study II, standardized coded packages with either 1200 IU or placebo (per capsule) olive oil capsules (Photo 1), (three packages per conscript, with 100 capsules per package) were manufactured on special order by Innopharma A/S (Denmark) (Photo 1.).

In Study III, standardized coded packages with either 600 IU or 4000 IU (per capsule) oil capsule were manufactured on special order by HC CLOVER PS, SL (Spain) in the same way.

In neither study was commercial sponsoring involved. The key to the package code numbers was stored in a computer database until the unblinding of the participants. At the end of both studies, all remaining packages and capsules were collected and destroyed.

Photo 1. Vitamin D oil capsules for the placebo group (left) and for the intervention group (right).

4.2.3 Side effects protocol

In Study II and Study III, personal protocols were prepared for registration of possible side effects of vitamin D supplementation. All participants were informed of side effects protocols, which were kept at the medical center of Kuperjanov Infantry Battalion.

4.2.4 Army Physical Fitness Test

The APFT was used to measure physical performance in Study I and Study III. All participants were informed about the rules of the test, including minimum and maximum scores with regards to the APFT guidelines. APFT physical performance testing took place on the same day, under the same conditions, on the same running track; this was done three times in both studies (Photo 2). The results were recorded, and the final result for each participant was calculated by the same experienced physical preparation coach at the Kuperjanov Infantry Battalion.

Photo 2. The APFT. Running 3.2 km (left), sit-ups (right) and push-ups (bottom).

4.2.5 Hand grip strength test

The hand grip strength test was performed using the same validated hydraulic hand dynamometer (Lafayette Instrument Co., United States) in all three studies (Photo 3.). Measurements were obtained from each participant in the standing position, arms at the side, not touching the body, with the elbow slightly bent (Photo 3). Each participant had to squeeze the dynamometer with as much force as possible. The best result (in kilograms) of three trials was recorded. The hand grip strength test was used in all studies. In Study I, the dominant hand grip strength was measured four times during study period. In Study II, both dominant and non-dominant hand grip strength were measured four times during the study period, and in Study III, dominant and non-dominant hand grip strength were measured three times during the study period.
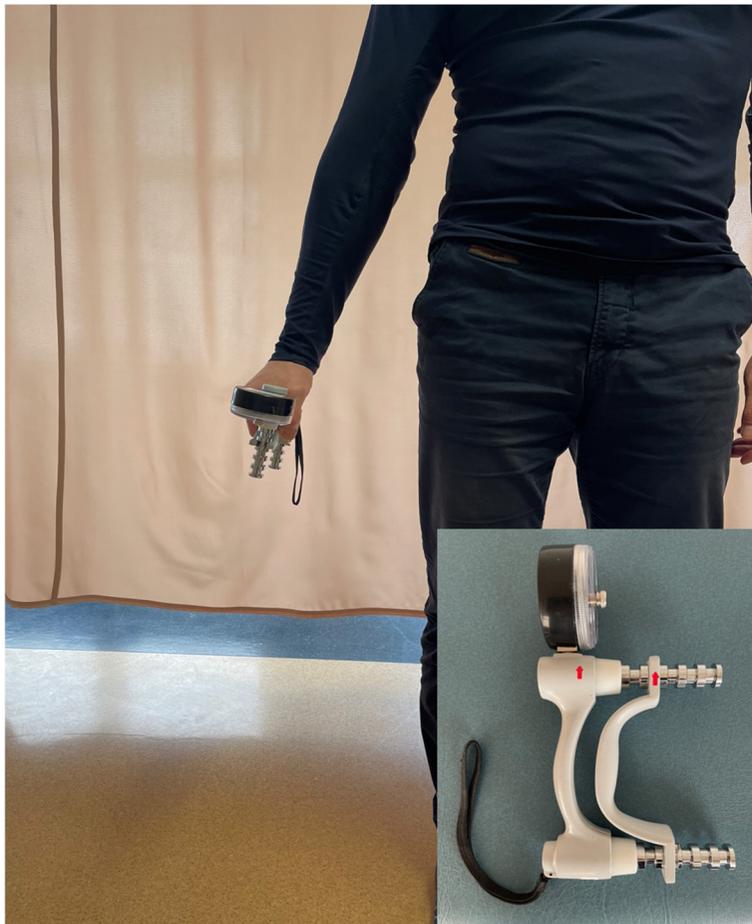

Photo 3. The hand grip strength test with dynamometer.

4.2.6 Blood serum tests and laboratory measurements

In Study I (Rips et al., 2023), a total of four blood serum analyses were done during the study period, including at baseline. All blood samples were overnight fasting tests, collected on the same day of the week each time, and all within the same hour of the day, under standardized conditions. Serum samples for clinical chemistry analysis were collected in serum clot activator tubes (BD Vacutainer SST II Advance Plus Blood Collection Tubes, Becton Dickinson and Company, New Jersey, United States). All analyses were performed by Synlab Estonia.

Blood serum values of vitamin D (25(OH)D) (> 75 nmol/l were classified as sufficient and < 25 nmol/l were classified as severe deficiency) were measured and obtained using the direct chemiluminescent immunoassay method (LIAISON XL, DiaSorin S.p.A, Saluggia VC, Italy). Blood serum parathyroid hormone measurements were performed using the direct chemiluminescent immunoassay method (ADVIA Centaur XP, Siemens Healthcare GmbH, Erlangen, Germany). Blood serum calcium measurements were performed using the spectrophoto-metry method (ADVIA® 1800 Clinical Chemistry System, Siemens Healthcare GmbH, Erlangen, Germany).

In Study II (Rips et al., 2022), a total of four blood serum analyses were done during the study period, including at baseline. All blood samples were overnight fasting tests, collected on the same day of the week each time, and all within the same hour of the day, under standardized conditions. Serum samples for clinical chemistry analysis were collected in serum clot activator tubes (BD Vacutainer SST II Advance Plus Blood Collection Tubes, Becton Dickinson and Company, New Jersey, United States). All analyses were performed by Synlab Estonia.

Blood serum values of vitamin D (25(OH)D) (> 75 nmol/l were classified as sufficient and < 25 nmol/l were classified as severe deficiency) were measured and obtained using the direct chemiluminescent immunoassay method (LIAISON XL, DiaSorin S.p.A, Saluggia VC, Italy). Blood serum parathyroid hormone measurements were performed using the direct chemiluminescent immunoassay method (ADVIA Centaur XP, Siemens Healthcare GmbH, Erlangen, Germany). Blood serum calcium measurements were performed using the spectrophoto-metry method (ADVIA® 1800 Clinical Chemistry System, Siemens Healthcare GmbH, Erlangen, Germany). Blood serum ionized calcium measurements were performed using ion-selective electrodes (AVL 9180 Electrolyte Analyzer, Roche Diagnostics, Germany). Blood serum testosterone measurements were performed using the direct chemiluminescent immunoassay method (ADVIA Centaur TSTII assay, Siemens Healthcare GmbH, Erlangen, Germany). Blood serum cortisol measurements were performed using the solid-phase competitive chemiluminescent enzyme immunoassay method (IMMULITE 2000 Cortisol, Siemens Healthcare Diagnostics Products Ltd. United Kingdom).

In Study III (Rips et al., 2024), a total of four blood serum analyses were done during the study period, including at baseline. All blood samples were overnight fasting tests, collected on the same day of the week each time, and all within the same hour of the day, under standardized conditions. Serum samples for clinical chemistry analysis were collected in serum clot activator tubes (BD Vacutainer SST II Advance Plus Blood Collection Tubes, Becton Dickinson and Company, New Jersey, United States). All analyses were performed by Synlab Estonia.

Blood serum values of vitamin D (25(OH)D) (> 75 nmol/l were classified as sufficient and < 25 nmol/l were classified as severe deficiency) were measured and obtained using the direct chemiluminescent immunoassay method (LIAISON XL, DiaSorin S.p.A, Saluggia VC, Italy). Blood serum parathyroid hormone measurements were performed using the direct chemiluminescent immunoassay method (ADVIA Centaur XP, Siemens Healthcare GmbH, Erlangen, Germany). Blood serum calcium measurements were performed using the spectrophotometry method (ADVIA® 1800 Clinical Chemistry System, Siemens Healthcare GmbH, Erlangen, Germany). Blood serum ionized calcium measurements were performed using ion-selective electrodes (AVL 9180 Electrolyte Analyzer, Roche Diagnostics, Germany).

4.3 Power analysis and statistical methods

In Study I (Rips et al., 2023), the serum level of 25(OH)D was the primary variable of the study. In the absence of available pilot data, a pragmatic decision was taken in the power analysis; a difference of 20 nmol/l (i.e. less than the increments of 25 nmol/l in the study by Funderburk et al. 2015) between the intervention and the control group was considered to be the meaningful detectable difference. With a standard deviation (SD) of 25 nmol/l, it would be necessary to follow 14 subjects over time to reach a power of 80%. To increase the power and allow for dropouts, over 80 subjects were initially recruited for the study.

Blood serum values, hand grip strength, and the physical fitness test results in the study group are described by means and standard deviations (SD). The comparison between time points was performed using a one-way ANOVA followed by pairwise t-tests with Bonferroni corrections used as post hoc tests to show significant differences. Distributions of categorical variables were described by absolute numbers and percentages and compared between groups using the two proportions Z-test. Statistical significance was set at $p < 0.05$. Furthermore, the participants were distributed into two subgroups for the last two measurements; those who had severe deficiency of 25(OH)D (< 25 nmol/l) and those who did not. Differences in the mean values of the variables of interest between the groups were evaluated using an unpaired t-test. Correlations between vitamin D levels and the variables of interest were calculated using Pearson correlation coefficients together with their p-values.

In Study II (Rips et al., 2022), the primary variable of the study was the level of 25(OH)D in the serum. In the absence of available pilot data, a pragmatic decision was taken in the power analysis; a difference of 20 nmol/l (i.e. less than the increments of 25 nmol/l in the study by Funderburk et al. 2015) between the intervention and the control group was considered to be the meaningful detectable difference. For example, with an SD of 25 nmol/l, then 26 participants would be needed in each group to reach a power of 80%. Correspondingly, for a difference in hand grip strength of 6 kilograms between the study groups, and an SD of 8 kilograms, then 29 participants would be needed in each group to reach a power of 80%. Initially, 65 participants were recruited to the study to allow for dropouts. Blood serum values and hand grip strength in the study groups were described by medians, ranges, means, and standard deviations (SD). Differences in mean values of the variables between the groups were evaluated using an ANOVA test followed by a Scheffe's post hoc test. The within-group comparisons over time were performed using a Repeated Measures ANOVA followed by a Scheffe's post hoc test. On all follow up occasions, the blood serum value of 25(OH)D was dichotomously classified as < 25 nmol/l (critically low) or not and was analyzed between the groups using a Fisher's exact test. For the primary variable, the 25(OH)D, the delta values at the follow-ups in relation to baseline values were calculated and reported as means and SDs. Statistical significance was set at $p < 0.05$.

In Study III (Rips et al., 2024), the primary variable of the study was the level of 25(OH)D in the serum. Based on the findings in Studies I and II, a difference of 20 nmol/l between the study groups was considered meaningful to measure. For example, for an SD of 25 nmol/l, 26 participants would be needed in each group to reach a power of 80%. Initially, 112 participants were included in the study to increase the power and to allow for dropouts.

Blood serum values, physical test results, and hand grip strength in the study groups were described by means and standard deviations (SD). Differences in mean values of the variables were evaluated using a two-way mixed measures ANOVA test with study group and time being the independent variables. Post hoc testing was done using a Tukey's test with estimated marginal means and Bonferroni correction within and between groups. Correlation between body weight and serum 25(OH)D levels was tested using a correlation test with Pearson correlation coefficients. Distribution of categorical variables was described using absolute numbers and percentages. Statistical significance was set at $p < 0.05$. For the assessment of outliers and the normality of data distribution, box plots and Shapiro–Wilk tests were used. The homogeneity of variances was checked using a Levene's test. In instances where the assumptions of parametric mixed ANOVA were not met, a robust alternative using trimmed means (bwtrim method) was applied.

4.4 Ethics

Study I (Rips et al., 2023) was approved by the Research Ethics Committee of the University of Tartu nos. 240/T-3 and 249M-4. The study was funded by grant no. R-001 (No 0.4-2.5/16/132) of the Estonian Defence Forces.

Study II (Rips et al., 2022) was approved by the Research Ethics Committee of the University of Tartu nos. 262/T-28 and 264M-14. The trial was retrospectively registered in ClinicalTrials.gov, Identifier: NCT04359524. The study was funded by grant no. R-002 (No. 0.4-2.5/16/1321) of the Estonian Defence Forces.

Study III (Rips et al., 2024) was approved by the Research Ethics Committee of the University of Tartu nos. 323/T-3, 337M-25, and 341M-12. The trial was prospectively registered in ClinicalTrials.gov, Identifier: NCT04939636. The study was funded by grant no. KVA-0.7-1./20/29041 of the Estonian Defence Forces.

5. RESULTS

5.1 Baseline anthropometric characteristics

All participants within the three studies were homogeneous with no significant differences between the groups. Also, age and anthropometric characteristics were similar in the three studies. Baseline anthropometric characteristics of all three studies are presented in Table 2.

Table 2. Anthropometric characteristics of participants in Studies I–III.

Study number	Study I	Study II			Study III		
Characte-ristics	Partici-pants	Inter-vention group	Placebo group	p-value	600 IU group	4000 IU group	p-value
Number of participants	86	27	26		55	57	
Age (years) Mean (SD)	21.0 (1.6)	20.8 (1.7)	21.2 (2.0)	n.s. 0.38	19.5 (1.3)	19.3 (0.9)	n.s. 0.22
Height (cm) Mean (SD)	182 (6.3)	180 (6.9)	179.0 (7.7)	n.s. 0.49	184 (6.1)	181 (5.7)	n.s. 0.06
Weight baseline (kg) Mean (SD)	79.9 (11.2)	74.0 (10.8)	74.5 (11.1)	n.s. 0.89	81.6 (14.4)	78.3 (13.6)	n.s. 0.21
BMI baseline (kg/m^2) Mean (SD)	24.2 (2.9)	22.7 (2.4)	23.2 (2.6)	n.s. 0.48	24.2 (4.2)	23.7 (3.6)	n.s. 0.48

Abbreviations: IU – international unit; SD – standard deviation; n.s. – non-significant; cm – centimeter; kg – kilogram; BMI – body mass index

5.2 Study I (Rips et al., 2023)

A decrease in blood serum 25(OH)D mean values was found, from 61.8 nmol/l at the baseline in July to 31.9 nmol/l in March (p < 0.001) (Table 3). Severe deficiency of vitamin D (< 25 nmol/l) was found in both July and September in 1/86 participants. Correspondingly, in December and March, 21/79 and 27/76 participants with severe deficiency were found, respectively. None of the participants reached the suggested sufficient level of 25(OH)D (> 75 nmol/l) in March (Figure 6).

At some time points during the study, blood serum PTH and Ca values showed significant differences compared to baseline; however, mean values were within normal ranges (Table 3).

In terms of the physical performance test and hand grip strength tests, no significant correlations with 25(OH)D levels were found, except for the hand grip strength and sit-up tests at baseline. All physical test results improved significantly compared to the baseline (Table 4).

No significant difference was found between those with blood serum 25(OH)D values < 25 nmol/l (cut-off value for severe deficiency) and > 25 nmol/l in terms of the hand grip strength and physical performance tests (Table 5).
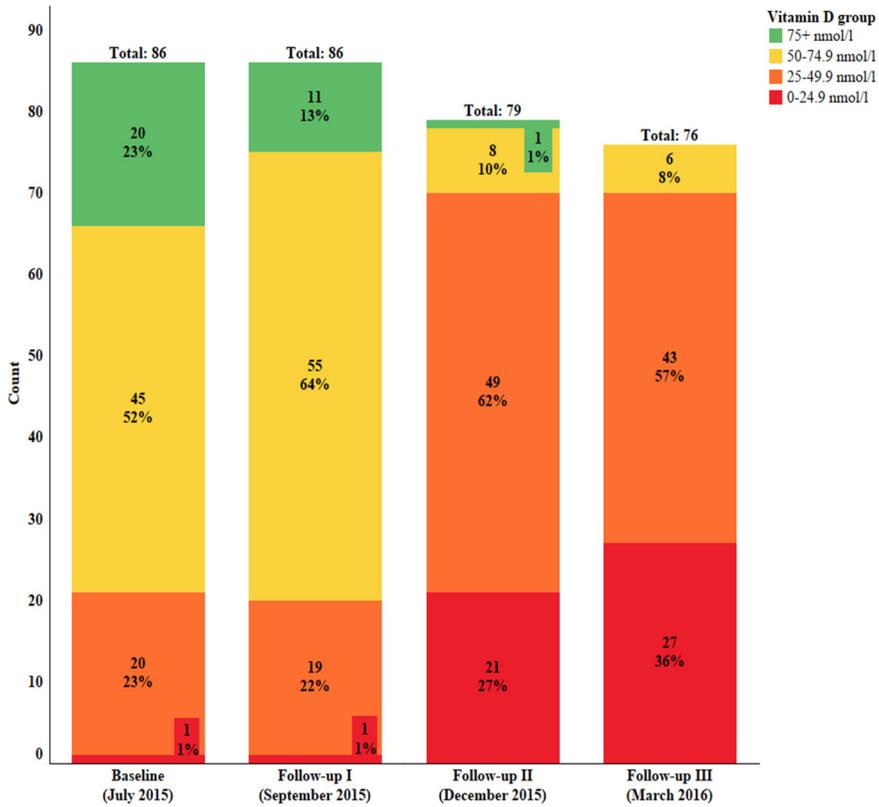
Figure 6. Study I. Distribution of conscripts' vitamin D 25(OH)D blood serum levels over time, showing increasing numbers of deficiency from 24% to 82% and severe deficiency from 1% to 36%, especially in the winter- and springtime. Low representation of sufficient 25(OH)D levels (23%) was detected in midsummer, with a rapid decrease to 0% in March.

Table 3. Study I. Blood test values over time. Significant blood serum 25(OH)D decrease over time was detected from the baseline in July to the final measurement in March. Parathyroid hormone and calcium mean values showed significant differences at some time points but within normative ranges of values.

Characteristics	Baseline (n = 86)	Follow-up I (~2 months) (n = 86)	Follow-up II (~5 months) (n = 79)	Follow-up III (~8 months) (n = 76)
Serum 25(OH)D level, nmol/l (recommended level >75 nmol/l)				
Median (range)	58.4 (23.3–121.0)	59.2 (24.7–89.2)	33.0 (14.0–79.3)	31.0 (14.6–67.2)
Mean (SD)	61.8 (18.6)	59.2 (13.5)	34.1 (12.8)	31.9 (12.0)
Missing values	0	0	7	10
Parathyroid hormone, pmol/l (normal 1.48–7.83 pmol/l)				
Median (range)	4.55 (1.2–14.3)	3.25 (1.4–9.6)	4.30 (2.0–11.2)	4.35 (1.6–10.7)
Mean (SD)	4.8 (2.1)	3.7 (1.5)	4.7 (2.0)	4.9 (2.0)
Missing values	0	0	7	10
Calcium, mmol/l (normal 2.15–2.6 mmol/l)				
Median (range)	2.52 (2.33–2.87)	2.49 (2.26–2.88)	2.41 (2.27–2.79)	2.46 (2.25–2.75)
Mean (SD)	2.5 (0.1)	2.5 (0.1)	2.4 (0.1)	2.5 (0.1)
Missing values	0	0	7	10

Pairwise comparisons

Measurement	BL vs FP I	BL vs FP II	BL vs FP III	FP I vs FP II	FP I vs FP III	FP II vs FP III
25(OH)D	0.269 (n.s.)	< 0.001	< 0.001	< 0.001	< 0.001	0.244 (n.s.)
PTH	< 0.001	1 (n.s.)	1 (n.s.)	< 0.001	< 0.001	1 (n.s.)
Ca	0.002	< 0.001	< 0.001	< 0.001	0.94 (n.s.)	< 0.001

Abbreviations: SD – standard deviation; PTH – parathyroid hormone; Ca – calcium; BL – baseline; FP – follow-up; n.s. non-significant

Table 4. Study I. Physical test results during the study period. Statistical significance was found in all physical test results between baseline and final follow-up.

Characteristics	Baseline (n = 86/85)	Follow-up I (~2 months) (n = 86)	Follow-up II (~5 months) (n = 83)	Follow-up III (~8 months) (n = 81)	Follow-up IV (~10 months) (n = 65)	p-values (pairwise comparisons)
Hand grip strength, kg (dominant)						
Median (range)	58 (40–86)	58 (44–92)		60 (43–92)		BL vs FP I: **< 0.001**
Mean (SD)	57.8 (8.2)	60.2 (8.5)		60.7 (8.5)		BL vs FP III: **0.001**
Missing values	0	0		5		FP I vs FP III: 1 (n.s.)
APFT scores (0–300)						
Median (range)	212 (26–300)		272 (166–300)		257 (141–300)	BL vs FP II:**< 0.001**
Mean (SD)	209.8 (50.3)		264.9 (29.6)		248.7 (35.8)	BL vs FP IV: **< 0.001**
Missing values	1		3		21	FP II vs FP IV: **< 0.001**
Running time, min						
Median (range)	15:00 (11:39–20:03)		13:36 (11:48–17:36)		14:25 (12:05–18:45)	BL vs FP II: **< 0.001**
Mean (SD)	15:17 (1:44)		13:51 (1:12)		14:31 (1:29)	BL vs FP IV: **0.008**
Missing values	1		3		21	FP II vs FP IV: **0.001**
Push-ups, number						
Median (range)	49 (9–91)		69 (30–105)		69 (38–103)	BL vs FP II: **< 0.001**
Mean (SD)	49.5 (17.5)		66.1 (13.9)		65.3 (12.6)	BL vs FP IV: **< 0.001**
Missing values	1		3		21	FP II vs FP IV: 0.50 (n.s.)
Sit-ups, number						
Median (range)	51 (7–85)		69 (27–95)		59 (36–87)	BL vs FP II: **< 0.001**
Mean (SD)	51.9 (15.8)		67.3 (12.9)		59.8 (12.7)	BL vs FP IV: **< 0.001**
Missing values	1		3		21	FP II vs FP IV: **< 0.001**
Passing test yes/no						
Count	58 (68) / 27 (32)		82 (99) / 1 (1)		60 (92) / 5 (8)	BL vs FP II: **< 0.001**
(%)						BL vs FP IV: **< 0.001**
Missing values	1		3		21	FP II vs FP IV: **< 0.001**

Abbreviations: SD – standard deviation; APFT – The Army Physical Fitness Test; BL – baseline; FP – follow-up; n.s. non-significant

Table 5. Study I. Physical test results at follow-ups II–IV divided into two subgroups. Group I had severe deficiency of vitamin D, with 25(OH)D values under 25 nmol/l, and Group II had vitamin D (25(OH)D) values over 25 nmol/l. None of the physical tests revealed any significant difference between participants in Group I with serum levels of 25(OH)D <25 nmol/l (Group I) and those with values >25 nmol/l (Group II) at follow-up II and follow-up III/IV.

	Follow-up II Group I 0–24 nmol/l (n = 21)	Follow-up II Group II 25+ nmol/l (n = 58)	Follow-up III/IV Group I 0–24 nmol/l (n = 27)	Follow-up III/IV Group II 25+ nmol/l (n = 49)	Follow-up II Pearson correlation test (p-value)	Follow-up III/IV Pearson correlation test (p-value)
Handgrip (dominant) Median (range) Mean (SD)	56 (44–70) 57.9 (8.2)	61 (44–92) 60.9 (8.6)	58 (44–92) 58.4 (10.0)	60 (43–83) 61.2 (7.1)	0.059 (n.s. 0.607)	0.119 (n.s. 0.30)
APFT (0–300) Median (range) Mean (SD) Missing values	258 (205–300) 258.5 (29.5) 0	276(166–300) 268.3(29.4) 0	250 (184–300) 246.5 (36.1) 3	258 (141–300) 250.1(36.0) 8	0.047 (n.s. 0.681)	-0.011 (n.s. 0.93)
Running time (min) Median (range) Mean (SD) Missing values	13:39 (12:06–16:15) 13:51 (1:08) 0	13:36 (11:48–17:12) 13:49 (1:11) 0	13:55 (12:05–17:36) 14:08 (1:21) 3	14:27 (12:22–18:45) 14:44 (1:32) 8	0.081 (n.s. 0.479)	0.243 (n.s. 0.051)
Push-ups Median (range) Mean (SD) Missing values	67 (40–88) 65.3 (14.1) 0	69.5 (30–105) 67.3 (13.8) 0	65.5 (38–86) 62.2 (11.8) 3	70 (42–103) 67.1 (12.9) 8	0.03 (n.s. 0.791)	0.157 (n.s. 0.21)
Sit-ups Median (range) Mean (SD) Missing values	65 (42–89) 65.2 (13.1) 0	70.5 (27–95) 68.3 (13.3) 0	58.5 (36–81) 57.8 (12.9) 3	59 (38–87) 61.0 (12.7) 8	0.138 (n.s. 0.224)	0.176 (n.s. 0.16)
Passing test yes/no (%) Missing values	21 (100) / 0 (0) 0	57 (98) / 1 (2) 0	23 (96) / 1 (4) 3	37 (90) / 4 (10) 8	-	-

Abbreviations: SD – standard deviation; APFT – The Army Physical Fitness Test; n.s. – non-significant

5.3 Study II (Rips et al., 2022)

The mean values of 25(OH)D showed no significant difference at the baseline between the study groups. At all other time points, blood serum 25(OH)D values were significantly higher in the intervention group (supplementation with 1200 IU) compared to the placebo group ($p < 0.001$) (Table 6). In the intervention group, blood serum 25(OH)D mean values did not change significantly during the study (Table 6).

Calcium, i-Ca, PTH, testosterone, and cortisol levels between the study groups are shown in Table 6.

In December, only 4/26 participants in the placebo group reached > 50 nmol/l. Correspondingly, in March and April, none of the participants in the placebo group reached > 50 nmol/l (Figure 7). The number of participants with severe deficiency (< 25 nmol/l) increased in the placebo group to 17/26 in March and 11/26 in April (Figure 7). No significant differences were found in the blood serum values of Ca in any time points between study groups.
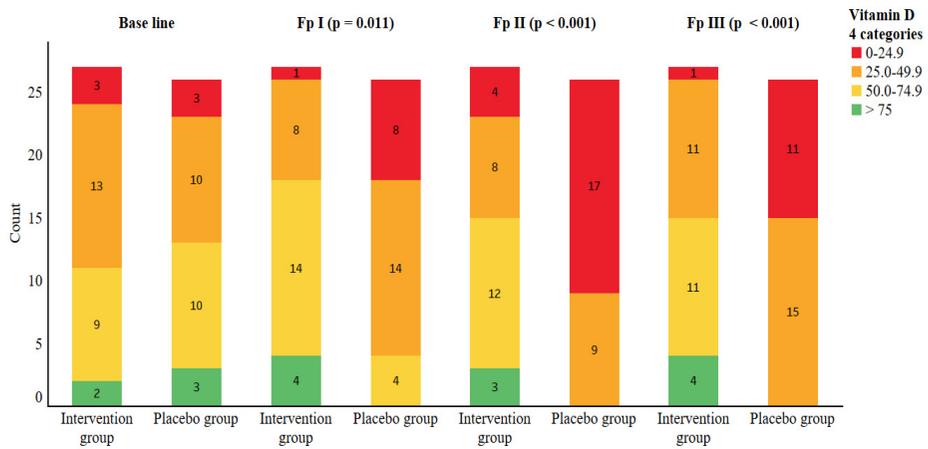
No significant differences were found in hand grip strength between the study groups at any time point (Table 7).

No side effects of supplementation with vitamin D were registered in the intervention group during the study period.

Table 6. Study II. Vitamin D 25(OH)D, PTH, testosterone, cortisol, calcium, and ionized calcium serum level results. Significant differences in blood serum 25(OH)D values were found between the intervention (1200 IU) and the placebo group at all three follow-ups. All other blood serum tests at all time points showed non-significant differences between the study groups.

Blood serum tests (normal values)	Baseline (October 2016)			Follow-up I (December 2016)			Follow-up II (March 2017)			Follow-up III (April 2017)		
	Intervention group	Placebo group	p-value	Intervention group	Placebo group	p-value	Intervention group	Placebo group	p-value	Intervention group	Placebo group	p-value
Vitamin D 25(OH)D (>75 nmol/l) Median (range) Mean (SD)	47.8 (19.3–93.9) 47.2 (18.6)	50.0 (22.3–88.7) 49.8 (20.0)	n.s. (0.63)	62.5 (19.1–91.0) 59.8 (15.9)	36.8 (15.9–66.9) 36.4 (14.2)	< 0.001	53.0 (12.1–88.4) 50.2 (19.8)	20.2 (11.1–37.3) 21.9 (7.7)	< 0.001	52.2 (18.6–89.1) 53.6 (18.3)	28.9 (16.9–49.9) 29.9 (9.3)	< 0.001
Vitamin D 25(OH)D Delta value compared to baseline (nmol/l)	NA	NA		12.5 (16.5)	-13.4 (9.8)		2.9 (15.2)	-27.9 (13.4)		6.3 (20.2)	-19.9 (12.7)	
Parathyroid hormone (1.48–7.83 pmol/l) Median (range) Mean (SD)	4.5 (1.7–10.1) 4.8 (2.2)	4.4 (0.9–9.9) 4.5 (2.4)	n.s. (0.60)	3.3 (0.8–7.4) 3.6 (1.7)	3.9 (0.7–12.9) 4.3 (2.4)	n.s (0.20)	4.3 (1.2–6.0) 3.9 (1.6)	4.3 (1.8–20.1) 5.0 (3.6)	n.s. (0.14)	4.5 (1.8–8.2) 4.7 (1.8)	4.3 (2.2–8.8) 4.9 (2.1)	n.s. (0.75)
Testosterone (8.4–28.7 nmol/l) Median (range) Mean (SD)	15.4 (10.8–29.6) 17.4 (5.3)	16.2 (6.1–31.0) 17.4 (5.7)	n.s. (0.99)	20.0 (5.2–26.6) 18.7 (5.3)	18.9 (11.7–30.0) 19.3 (4.0)	n.s (0.65)	19.1 (8.3–26.0) 18.5 (4.2)	21.0 (5.7–28.4) 20.5 (4.8)	n.s. (0.12)	20.5 (10.1–32.5) 21.3 (5.9)	20.1 (13.0–28.4) 20.3 (4.1)	n.s. (0.48)
Cortisol (138–690 nmol/l) Median (range) Mean (SD)	527.0 (400–615) 517.3 (62.7)	506.5 (348–670) 513.7 (69.8)	n.s. (0.85)	538.0 (450–756) 554.0 (70.1)	561.5 (292–676) 536.1 (91.6)	n.s (0.43)	452.0 (251–629) 457.7 (105.1)	452.5 (114–577) 438.8 (94.4)	n.s. (0.50)	488.0 (265–668) 482.4 (85.8)	473.5 (287–599) 470.3 (76.6)	n.s. (0.59)
Calcium (2.15–2.6 mmol/l) Median (range) Mean (SD)	2.37 (2.28–2.50) 2.39 (0.07)	2.38 (2.23–2.53) 2.37 (0.07)	n.s. (0.30)	2.28 (2.18–2.36) 2.28 (0.05)	2.25 (2.13–2.43) 2.26 (0.06)	n.s (0.22)	2.36 (2.29–2.48) 2.36 (0.05)	2.36 (2.24–2.46) 2.35 (0.06)	n.s. (0.61)	2.29 (2.11–2.42) 2.28 (0.08)	2.26 (2.12–2.34) 2.24 (0.05)	0.05
Calcium ionized (1.12–1.32 mmol/l) Median (range) Mean (SD)	1.23 (1.15–1.31) 1.23 (0.04)	1.22 (1.15–1.28) 1.21 (0.03)	n.s. (0.23)	1.25 (1.20–1.32) 1.25 (0.03)	1.24 (1.17–1.32) 1.25 (0.04)	n.s (0.58)	1.23 (1.08–1.33) 1.22 (0.04)	1.23 (1.18–1.28) 1.23 (0.03)	n.s. (0.58)	1.23 (1.18–1.29) 1.24 (0.03)	1.23 (1.15–1.29) 1.23 (0.03)	n.s. (0.37)

Abbreviations: SD – standard deviation; n.s.– non-significant

Abbreviations: Fp – follow-up.

Figure 7. Study II Distribution of vitamin D blood serum 25(OH)D levels in the intervention group (1200 IU supplementation) and placebo group over the study period according to categories based on the Endocrine Society (Holick et al. 2011) and Funderburk (Funderburk et al. 2015). Significantly more severe deficiencies were found in the placebo group at all follow-ups – December 31%, March 65%, and April 42% – with none of the participants having sufficient levels. However, a minor increase in blood serum 25(OH)D levels was found in the 1200 IU supplementation group at all follow up occasions compared to baseline.

43

Table 7. Study II. Hand grip strength results for both hands during the study period. No statistically significant differences were found between the study groups at any time point.

	Baseline (October 2016)			Follow-up I (December 2016)			Follow-up II (March 2017)			Follow-up III (April 2017)		
	Intervention group	Placebo group	p-value	Intervention group	Placebo group	p-value	Intervention group	Placebo group	p-value	Intervention group	Placebo group	p-value
Hand grip right **Median (range)** **Mean (SD)**	48.0 (29–72) 48.0 (9.8)	50 (28–72) 49.1 (10.2)	n.s (0.70)	50.0 (30–65) 50.1 (7.6)	50.0 (30–70) 50.8 (8.5)	n.s. (0.74)	52.0 (30–80) 52.6 (9.6)	53.0 (30–70) 52.5 (10.0)	n.s. (0.97)	51.0 (28–84) 51.0 (9.0)	50.5 (34–68) 51.8 (9.0)	n.s. (0.78)
Hand grip left **Median (range)** **Mean (SD)**	46.0 (32–66) 45.9 (8.3)	50.0 (29–68) 47.8 (9.3)	n.s. (0.45)	48.0 (32–60) 47.9 (6.7)	49.0 (32–70) 49.5 (9.3)	n.s. (0.48)	50 (38–68) 50.8 (7.3)	52.0 (32–70) 50.8 (8.9)	n.s. (0.99)	49.0 (38–75) 49.9 (9.2)	50.0 (32–66) 50.7 (8.9)	n.s. (0.76)

Abbreviations: SD – standard deviation; n.s. – non-significant

5.4 Study III (Rips et al., 2024)

The mean values of blood serum 25(OH)D values were significantly lower in the 600 IU group compared to the 4000 IU group except at baseline (p < 0.001), with a mean blood serum 25(OH)D value of 46.1 nmol/l in the 600 IU group and 69.8 nmol/l in 4000 IU group at the end of the study in May (Table 8). Of the 53 participants in the 4000 IU group, 34 reached the sufficient level (> 75 nmol/l) of blood serum 25(OH)D in October, which decreased to 19 of 50 participants in May. In the 600 IU group, 22/55 had sufficient levels of 25(OH)D at baseline, 8/50 did in October, and none did in January or in May (Figure 8). No significant differences were found in PTH, Ca, or i-Ca blood serum levels between study groups at any time point except for the Ca values in the 4000 IU group at one time point (p = 0.04) during the study period (Table 8). In terms of body weight, no significant correlation was found between body weight and blood serum 25(OH)D values during the study period. No significant differences were found between the study groups at any time point in terms of physical fitness tests or hand grip strength tests (Tables 9–10).

No side effects of supplementation with vitamin D were registered in either group during the study period.
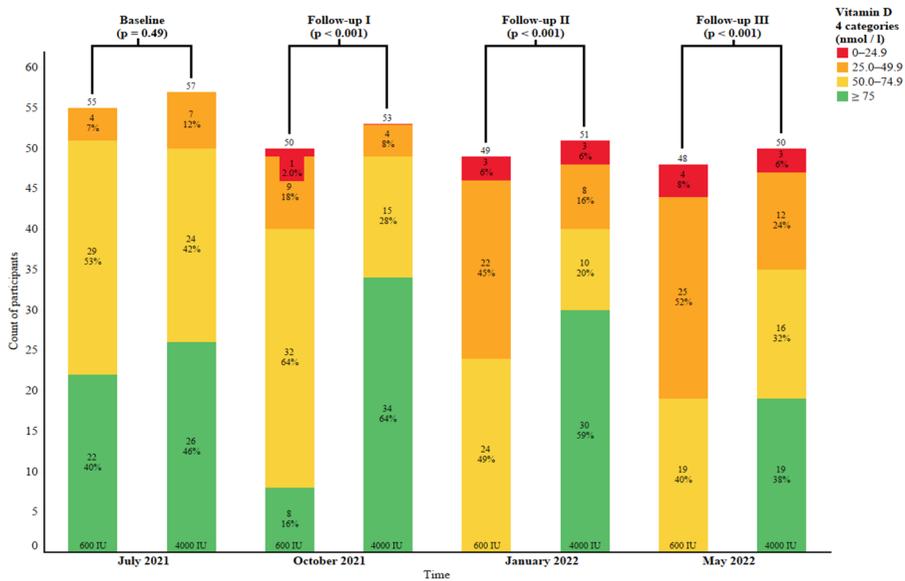

Figure 8. Study III Distributions of vitamin D blood serum 25(OH)D levels in both study groups showing no participants with sufficient levels in the 600 IU supplementation group in January and May. In the 4000 IU group, sufficient blood serum 25(OH)D levels were found in October in 64% of participants, with a future decrease to 38% in May.

Table 8. Study III Blood test values over time. There was a significant decrease in 25(OH)D values in the 600 IU group, blood serum 25(OH)D values were stable during the study period. A rise in mean PTH and i-Ca values were found in both study groups, and a decrease in Ca was found in both study groups, with significant differences over time – however, within normative values.

Characteristics	Baseline (July 2021) (n = 112) — 600 IU n = 55	Baseline — 4000 IU n = 57	Baseline — BW groups	Follow-up I (October 2021) (n = 103) — 600 IU n = 50	FUI — 4000 IU n = 53	FUI — BW groups	FUI — WI group B vs. FUI	Follow-up II (January 2022) (n = 100) — 600 IU n = 49	FUII — 4000 IU n = 51	FUII — BW groups	FUII — WI group B vs. FUII	FUII — WI group FUI vs. FUII	Follow-up III (May 2022) (n = 98) — 600 IU n = 48	FUIII — 4000 IU n = 50	FUIII — BW groups	FUIII — WI group B vs. FUIII	FUIII — WI group FUII vs. FUIII	Two-way mixed ANOVA — Within subjects, whole study group, time
Serum 25(OH)D level, nmol/l (recommended level > 75 nmol/l) Mean (SD) Missing values	77.3 (30.09) 0	74.0 (20.08) 0	n.s.	60.6 (14.91) 5	84.6 (23.16) 4	< 0.001	600 IU < 0.001; 4000 IU = 0.01	49.1 (14.00) 6	75.3 (26.96) 6	< 0.001	600 IU < 0.001; 4000 IU n.s.	600 IU = 0.003; 4000 IU = 0.03	46.1 (12.88) 7	69.8 (30.82) 7	< 0.001	600 IU < 0.001; 4000 IU n.s.	600 IU n.s.; 4000 IU n.s.	**Effects:** Time: **< 0.001**
Parathyroid hormone, pmol/l (normal 1.48–7.83 pmol/l) Mean (SD) Missing values	3.29 (1.97) 0	2.67 (1.21) 0	n.s.	3.81 (3.17) 5	2.95 (0.98) 4	n.s.	600 IU n.s.; 4000 IU n.s.	4.57 (4.39) 6	3.88 (1.66) 6	n.s.	600 IU < 0.001; 4000 IU < 0.001	600 IU = 0.04; 4000 IU = 0.003	4.15 (2.98) 7	3.05 (1.53) 7	n.s.	600 IU = 0.04; 4000 IU n.s.	600 IU n.s.; 4000 IU = 0.02	Effects: Time: < 0.001
i-Ca, ionized calcium, mmol/l (normal 1.12–1.32 mmol/l) Mean (SD) Missing values	1.17 (0.03) 0	1.17 (0.04) 0	n.s.	1.23 (0.03) 5	1.24 (0.04) 4	n.s.	600 IU < 0.001; 4000 IU < 0.001	1.20 (0.03) 7	1.21 (0.04) 6	n.s.	600 IU < 0.001; 4000 IU < 0.001	600 IU < 0.001; 4000 IU = 0.002	1.24 (0.03) 7	1.24 (0.08) 7	n.s.	600 IU < 0.001; 4000 IU < 0.001	600 IU < 0.001; 4000 IU = 0.006	**Effects:** Time: **< 0.001**
Calcium, mmol/l (normal 2.15–2.6 mmol/l) Mean (SD) Missing values	2.53 (0.07) 0	2.54 (0.07) 0	n.s.	2.39 (0.08) 5	2.40 (0.07) 4	n.s.	600 IU < 0.001; 4000 IU < 0.001	2.37 (0.08) 6	2.41 (0.07) 6	n.s.	600 IU < 0.001; 4000 IU < 0.001	600 IU n.s.; 4000 IU n.s.	2.34 (0.07) 7	2.37 (0.09) 7	n.s.	600 IU < 0.001; 4000 IU < 0.001	600 IU n.s.; 4000 IU = 0.001	**Effects:** Time: **< 0.001**

Abbreviations: IU – international unit; BW groups – between groups; WI group – within group; B – baseline; FUI – Follow-up I; FUII – Follow-up II; FUIII – Follow-up III; SD – standard deviation; n.s. – non-significant

Table 9. Study III Physical test results. No significant differences between the study groups at any time points were shown in the physical fitness tests. All physical test results improved over time compared to baseline.

Characteristics	Baseline (July 2021) (n = 106) Post hoc analysis p-values			Follow-up I (October 2021) (n = 106) Post hoc analysis p-values				Follow-up II (May 2022) (n = 82) Post hoc analysis p-values					Two-way mixed ANOVA
	600 IU n = 50	4000 IU n = 56	BW groups	600 IU n = 51	4000 IU n = 55	BW groups	WI group B vs. FUI	600 IU n = 41	4000 IU n = 41	BW groups	WI group B vs. FUII	WI group FUI vs. FUII	Within subjects, whole study group, time
APFT scores (0–300) Mean (SD) Missing values	173.3 (52.5) 5	174.1 (60.6) 1	n.s.	219.9 (47.7) 4	220.8 (52.9) 2	n.s.	600 IU < 0.001 4000 IU < 0.001	195.3 (47.2) 14	204.2 (49.0) 16	n.s.	600 IU n.s. 4000 IU < 0.001	600 IU < 0.001 4000 IU < 0.001	**Effects:** Time: **< 0.001**
Running time (min) Mean (SD) Missing values	17:36 (3:29) 8	17:19 (3:39) 3	n.s.	15:09 (1:43) 5	15:01 (1:50) 3	n.s.	600 IU < 0.001 4000 IU < 0.001	17:22 (3:43) 15	16:52 (3:55) 16	n.s.	600 IU n.s. 4000 IU n.s.	600 IU < 0.001 4000 IU < 0.001	**Effects:** Time: **< 0.001**
Push-ups, (number) Mean (SD) Missing values	45 (15.0) 5	43 (16.3) 1	n.s.	55 (13.0) 4	58 (15.2) 3	n.s.	600 IU < 0.001 4000 IU < 0.001	54 (12.3) 14	54 (13.7) 16	n.s.	600 IU = 0.001 4000 IU < 0.001	600 IU n.s. 4000 IU n.s.	**Effects:** Time: **< 0.001**
Sit-ups, (number) Mean (SD) Missing values	48 (13.1) 5	48 (15.2) 1	n.s.	56 (12.5) 4	57 (13.5) 3	n.s.	600 IU < 0.001 4000 IU < 0.001	54 (12.1) 14	56 (14.4) 16	n.s.	600 IU n.s. 4000 IU = 0.02	600 IU n.s. 4000 IU n.s.	**Effects:** Time: **< 0.001**
Passing test yes/no (%) Missing values	11/39 (22) 5	16/40 (29) 1		42/9 (82) 4	43/12 (78) 2			15/26 (37) 14	20/21 (49) 16				

Abbreviations: IU – international unit; BW groups – between groups; WI group – within group; B – baseline; FUI – Follow-up I; FUII – Follow-up II; FUIII – Follow-up III; SD – standard deviation; APFT – Army Physical Fitness Test; n.s. – non-significant

Table 10. Study III Hand grip strength test results. No significant differences between the study groups at any time point were shown in the hand grip strength tests. A significant decrease in hand grip strength was found over time in both study groups.

Characteristics	Baseline (July 2021) (n = 112) Post hoc analysis p-values			Follow-up I (October 2021) (n = 102) Post hoc analysis p-values				Follow-up II (January 2022) (n = 100) Post hoc analysis p-values					Two-way mixed ANOVA
	600 IU n = 55	4000 IU n = 57	BW groups	600 IU n = 50	4000 IU n = 52	BW groups	WI group B vs FUI	600 IU n = 49	4000 IU n = 51	BW groups	WI group B vs. FUII	WI group FUI vs. FUII	Within subjects, whole study group, time
Grip test dominant hand, (kg) Mean (SD) unit Missing values	46.3 (8.1) 0	44.3 (7.6) 0	n.s.	45.4 (8.0) 5	43.6 (6.8) 5	n.s.	600 IU n.s. 4000 IU n.s.	44.1 (8.2) 6	43.6 (8.4) 6	n.s.	600 IU = 0.04 4000 IU n.s.	600 IU n.s. 4000 IU n.s.	**Effects:** Time: **0.012**
Grip test non-dominant hand, (kg) Mean (SD) unit Missing values	44.3 (8.5) 0	41.4 (7.7) 0	n.s.	42.9 (7.8) 5	43.1 (8.5) 4	n.s.	600IU n.s. 4000IU = 0.03	41.8 (8.6) 7	40.3 (8.1) 6	n.s.	600 IU = 0.01 4000 IU n.s.	600 IU n.s. 4000 IU < 0.001	**Effects:** Time: **< 0.001**

Abbreviations: IU – international unit; BW groups – between groups; WI group – within group; B – baseline; FUI – Follow-up I; FUII – Follow-up II; FUIII – Follow-up III; SD – standard deviation; n.s. – no

6. DISCUSSION

The main finding of this thesis is that long term supplementation with 4000 IU vitamin D decreases the risk of vitamin D deficiency and maintains sufficient levels better compared to vitamin D supplementation of 1200 IU and 600 IU in Estonian male conscripts during military service. However, neither vitamin D supplementation nor vitamin D status influence physical performance during military service in Estonian male conscripts.

6.1 Current status of vitamin D worldwide and in young Estonian male conscripts

Vitamin D deficiency is very common in both the general population (Cashman & Kiely, 2014; Henriques et al., 2022; Holick et al., 2011; Lamberg-Allardt et al., 2013; Lips et al., 2019) and, more specifically, in the military community (Armstrong et al., 2020; Henriques et al., 2023; Laaksi et al., 2007) worldwide. It has also been shown that for people living at higher latitudes, vitamin D deficiency occurs more often during the winter and spring seasons (Spiro & Buttriss, 2014). In a study of male Royal Marines, a group with stress fractures (51 cases) showed significantly lower 25(OH)D blood serum values, with a mean value of 52.4 nmol/l, compared to 57.7 nmol/l in a control group without fractures (Armstrong et al., 2020). A study of 1569 male US Army recruits found significantly greater vitamin D deficiency in a group in which skipping breakfast was more common (Fagnant et al., 2022). In a systematic review by Henriques et al. (2023), which included 13 studies from northern hemisphere navies and submariners, a high prevalence of vitamin D deficiency was found. Fogleman et al. (2022) stated that based on current studies, vitamin D deficiency is very common in the military and that urgent action should be taken to prevent bone injuries. A large military-population-based study in the United States found that the overall rate of clinically diagnosed vitamin D deficiency was only 53.7 cases/100,000 person years (Knapik et al., 2021). In the Finnish Army, a study of 220 conscripts found vitamin D deficiency in 0.9% of soldiers in the summertime and 38.9% in wintertime (Välimäki et al., 2004). A study based on Estonian conscripts found an increasing rate in vitamin D deficiency defined as < 50 nmol/l from 42.6% at baseline to 91.5% 15 weeks into active service (Ööpik et al., 2017). A high rate of vitamin D deficiency was found also in an Estonian population-based study in which the mean value of blood serum 25(OH)D was 43.7 nmol/l in wintertime (Kull et al., 2009). This indicates a high prevalence of vitamin D deficiency among the Estonian population. Based on studies I and II, included in this thesis, high risk of vitamin D deficiency also occurs in summertime and increases rapidly in winter- and springtime without supplementation in conscripts.

To illustrate cut-off levels for blood serum 25(OH)D levels, a coloured diagram based on previous studies was developed and used in the studies included

in this thesis (Figure 2). In Study I, interestingly, sufficient levels (> 75 nmol/l) of blood serum 25(OH)D were found only in 23/86 conscripts in July. Based on our classification, for which the cut-off for deficiency is < 75 nmol/l, a high level of vitamin D deficiency was found already in September, and more critical deficiency and severe deficiency had increased up to 92% by March (Rips et al., 2023). These findings are supported by data from Study II, in which the placebo group of 26 conscripts had a rapid decrease in mean values of blood serum 25(OH)D from 50.0 nmol/l in October to 20.2 nmol/l in March. None of the participants had reached a sufficient level in December (Rips et al., 2022). Based on both these studies, a high risk of vitamin D deficiency already occurs in summertime, with a rapid increase in winter- and springtime among the Estonian young healthy male population participating in military service.

6.2 Severe vitamin D deficiency

There are only a few studies focusing on severe vitamin D deficiency in the physically active population. To define severe deficiency, two cut-off values are mainly used. Some authors set the cut-off limit of blood serum 25(OH)D at 30 nmol/l (Amrein et al., 2020) and some at 25 nmol/l (Allison et al., 2015). In both cases, severe deficiency of vitamin D dramatically increases the risk of excess mortality, infections, osteoporosis, stress fractures, and many other diseases (Kuo et al., 2022). Frequency of severe deficiency among 506 national-level athletes in a pair of studies was shown to vary from 11% (Allison et al., 2015) to 21.7% (Amrein et al., 2020). In all three studies in this thesis, < 25 nmol/l was used as the cut-off value determining severe deficiency of blood serum 25(OH)D, and a much higher rate of severe deficiency was found compared other studies. In Study I, severe deficiency was found in only 1% of participants in July, but there was a rapid increase up to 35.5% by March (Rips et al., 2023). In Study II, 11% of participants in both the placebo and the 1200 IU supplementation groups showed severe deficiency at baseline in October, with a rapid increase in the placebo group up to 65% by March (Rips et al., 2022). In Study III, in which both groups received supplementation, severe deficiency occurred in fewer participants – only 6% in January and 8% in May – regardless of group (Rips et al., 2024). Based on these three studies, a high prevalence of severe vitamin D deficiency occurs in conscripts during military service, with a rapid increase in winter- and springtime. Supplementation with vitamin D decreases the risk of severe deficiency in these conscripts in the Estonian Army.

6.3 Effect of vitamin D supplementation on blood serum 25(OH)D levels during military service

To decrease the risk of vitamin D deficiency, different supplementation protocols are recommended. The daily recommended dietary allowance or adequate intake (including supplementation) is often 600 IU in adults (Table 1), (Dietary Reference Values for Vitamin D EFSA, 2016; Holick et al., 2011; Lamberg-Allardt et al., 2013). However, some studies suggest a safe upper vitamin D supplementation limit to be much higher, up to 4000 IU in adults (Holick et al., 2011; Płudowski et al., 2023). Generally, supplementation has more consensus, but the daily safe dosage is still under debate (Cashman & Kiely, 2014). In a study by Carswell et al. (2018) a combination supplementation of four weeks of 1000 IU and eight weeks of 400 IU decreased vitamin D deficiency up to 97% in 967 military recruits. In this study, the cut-off value for deficiency was set to 50 nmol/l for blood serum 25(OH)D. In an eight-week study of 100 military recruits during basic training, supplementation with 800 IU increased mean blood serum 25(OH)D values from 22.5 to 31.0 ng/ml (56.25–77.5 nmol/l) (Gaffney-Stomberg et al., 2022). A Finnish study with 164 conscripts concluded that six months supplementation with 400 IU of vitamin D in wintertime kept mean values of blood serum 25(OH)D to 78.7 nmol/l at baseline and 71.6 nmol/l at six months; this was significantly different compared to a placebo group with a mean blood serum 25(OH)D value of 51.3 nmol/l ($p < 0.001$) at six months (I. Laaksi et al., 2010). In a study of 131 soldiers in the US Army, two dosages of vitamin D were compared. A low dosage of 1000 IU and high dosage of 5000 IU were used during three months of supplementation. The result was mean blood serum 25(OH)D values of 40.15 ng/ml (100.3 nmol/l) in the 5000 IU group and 30.80 ng/ml (77 nmol/l) in the 1000 IU group. Based on the findings in Study II, a seven-month supplementation with 1200 IU vitamin D kept blood serum 25(OH)D mean values close to baseline values, with 47.8 nmol/l in October and 52.2 nmol/l in April; for comparison, a significant decrease in blood serum 25(OH)D, down to 28.9 nmol/l in April, was found in the placebo group (Rips et al., 2022). In Study III, two different vitamin D dosages, 600 IU and 4000 IU, were used. In the 600 IU group, a rapid decrease in the blood serum 25(OH)D mean value was found – 46.1 nmol/l in May, compared to 69.8 nmol/l in the 4000 IU group (Rips et al., 2024). Based on the two supplementation studies included in this thesis using a total of three different dosages, sufficient levels of vitamin D > 75 nmol/l were not achieved with 600 IU or 1200 IU. In the group supplemented with 4000 IU, sufficient levels were achieved in 46% of participants in July and 38% in May. This could mean that the need for vitamin D increases during military training, and supplementation with 4000 IU is needed to keep blood serum 25(OH)D at an acceptable level, especially since there were no registered side effects of this treatment. No side effects were detected during the supplementation studies.

6.4 Physical fitness and vitamin D

To increase physical fitness of sportsmen and soldiers, the scientific community is looking for legal not banned methods. Vitamin D is a hormone-like bioactive molecule that has receptors in almost all tissues in the human body, including muscle cells; thus, a positive interaction with physical performance could be possible. Until now, only a few studies have found positive effects on physical performance related to vitamin D. Heileson et al. (2022) found that vitamin D levels are related to the results of physical tests in military recruits. Mason et al. (2019) found that low levels of vitamin D negatively affect muscle function in wintertime. Carswell et al. (2018) found positive effects of vitamin D supplementation on endurance performance. However, most studies could not show a positive influence of vitamin D on physical performance. Based on all three studies included in this thesis, vitamin D levels or supplementation has no positive effect on physical performance in terms of the APFT or hand grip strength in Estonian conscripts. Even severe deficiency of vitamin D did not reveal any negative effect on physical performance. However, all three studies found a positive effect of training on the physical test results (Rips et al., 2022, 2023, 2024).

6.5 Other parameters related to vitamin D measured in Studies I–III

PTH together with vitamin D are related to Ca and i-Ca metabolism (Khundmiri et al., 2016). Long-term vitamin D deficiency could affect calcium metabolism negatively. In cases of severe deficiency or deficiency of vitamin D, Study I showed that PTH values above normal were not related to abnormally high values of Ca, but rather to low serum 25(OH)D levels. In Study II, no significant changes in PTH levels were detected over time. In Study III, minimal changes outside of normative values of PTH, i-Ca, and Ca in the serum were found, with no signs of side effects. Low 25(OH)D levels increase PTH levels and calcium release from the bone (Rajab, 2022). In Study III, an increase in PTH was found in the 600 IU group, which had lower mean values of 25(OH)D, while more stable PTH values were found in the 4000 IU group, which had higher 25(OH)D values. Interestingly, seasonal variation in PTH was described previously in a large cohort study (Shen et al., 2020).

Testosterone and cortisol have crucial roles in muscle fitness (Casto & Edwards, 2016) and it has been shown that vitamin D is linked positively to testosterone production in the human body (Chen et al., 2019; Nimptsch et al., 2012). Cortisol is known as a stress hormone and also has an important role in regulating muscle function. Increased cortisol levels can decrease physical performance (Kramer et al., 2020; Duclos et al., 2003).

Based on the results of Study II, no significant differences between the study groups were found in either testosterone or cortisol levels at any time point. This

might be due to the fact that the study groups were small or that summertime monitoring was not performed.

A body mass index (BMI) > 30 kg/m^2 is a risk factor for low 25(OH)D levels (Brock et al., 2010; Funderburk et al., 2015). In Study III, no negative correlation between body weight and 25(OH)D blood serum levels was found, except for a weak negative correlation for the combined study group at baseline. However, in some cases, BMI might not the best tool to assess physical performance capacity. Potter et al. (2022) found that a BMI of 33.0 in fit marines was not related to the amount of fat, but rather to muscle, and these subjects were considered physically fit for extreme conditions. In Study III, an increase in body mass was found over time in both study groups, and most of the participants could falsely be considered pre-obese based on the WHO body mass index (BMI) classification.

6.6 Strengths and limitations

Study I. (Rips et al., 2023)
The key strength of Study I is the relatively long 10-month follow-up period that covers almost a full year and the entire training period for Estonian Army conscripts. A further strength is the clearly defined and homogeneous study groups with similar physical activity level, living conditions, clothing, and daily food intake during the whole study period. This enabled us to investigate vitamin D serum levels, and the APFT and hand grip strength outcomes in a standardized fashion.

Possible limitations of the study involve the small number of participants and limited number of physical performance tests. The fact that 24% of participants missed the final APFT is another limitation. Furthermore, the unknown dietary consumption of vitamin D during the study and that only baseline body mass was measured is also a potential limitation. That only men participated in the study, and that the last physical fitness test, hand grip strength test, and blood test session were not performed at the same time are limitations.

Study II. (Rips et al., 2022)
The strengths of Study II are its randomized and blinded design, the homogeneous test groups, and the follow-up period over the whole winter season with four physical performance test occasions. The study population was well standardized in terms of conditions, such as the season of the year, age, sex, daily food consumption, clothing, and physical activity. This provided an ideal opportunity to study the effect of vitamin D supplementation on serum levels of 25(OH)D and physical performance in the form of the hand grip strength test.

The limitations of the study include the small groups, relatively short only winter- and springtime follow-up of seven months, the use of only one supplementation dosage and one physical performance test, and the exclusion of female subjects. Also, the lack of lean body mass measurements and registration of

general health problems such as acute respiratory infections could be considered a limitation. Due to dropouts, the study is underpowered for the secondary outcome variable, the hand grip strength test. Also, the hand grip strength test might be a less sensitive test in the young population; lots of participants obtain high scores and an improvement might be hard to detect. Due to the expected seasonal variation of serum levels of 25(OH)D, the authors decided not to use the intention-to-treat principle, and only analyzed those participants who attended all follow-ups, which also can be considered a weakness. Furthermore, many conscripts chose not to participate. However, it can be assumed that there are either no or only small differences between conscripts because of the homogeneity of soldiers in the Estonian Army. Lastly, the generalizability of the study is limited to military personal in relatively high northern or southern latitudes.

Study III. (Rips et al., 2024)
The strengths of Study III study are its randomized and blinded design and that the long 10-month follow-up period included all seasons, starting from July and ending at the end of May. All physical activities included similar physical preparation and physical testing system. Standard military clothing was mandatory for all the participants during the study period despite seasonal changes. The food consumption was standardized and controlled by an Estonian Army dietitian. The age and sex of the participants were also standardized. The limitations of the study include the relatively small groups compared to larger cohort studies, the relatively high dropout rate, absence of a placebo group, the relatively high number of missed physical tests, and a possible non-compliance of daily vitamin D supplementation, in spite of vigorous monitoring. Furthermore, lack of a body composition assessment, and that no hand grip strength test was performed in late spring can also be considered limitations.

6.7 Scientific novelty and clinical relevance

This is the first time that vitamin D levels have been evaluated in Estonian young healthy male individuals across all seasons. Moreover, this is the first time that vitamin D supplementation effects of different dosages have been evaluated in the same population during all seasons in Estonia. The main finding of this thesis is that there is a high risk of vitamin D deficiency in all seasons, especially in winter- and springtime. A further important finding is that low dosage supplementation of vitamin D has little effect on vitamin D levels. Based on our findings, new supplementation guideline recommendation should be developed for young healthy males in Estonia.

6.8 Final considerations and future perspectives

This work is based on the Estonian young male population and covers an almost 10-year period of different studies concerning vitamin D measurement and supplementation over different seasons. Despite improving life standards, with better clothing, more sophisticated equipment, highly computerized technical solutions, and well-prepared food, we still face an interesting negative side effect of nature – lack of vitamin D. We see that the natural production of human vitamin D varies widely depending on the season and also from person to person. Interestingly, low values of serum 25(OH)D (vitamin D) can even be seen in the summertime, despite plenty of sun exposure; this might be related to more indoor activities with less sun exposure. This leads, in some cases, to very low values of vitamin D across all seasons. During our studies, we could not measure the long-term effects of vitamin D deficiency. It is known that vitamin D plays a crucial role in many body functions in humans; however, it appears that in the short term, the body has some resistance to vitamin D deficiency. Late consequences, seen after decades, involve a higher risk of osteopenia, osteoporosis, and other health issues. All subjects in the study groups of this thesis were at the life stage at which an increase in bone mass is still possible. Lack of vitamin D may prevent the human body from increasing bone mass. Physical performance is another crucial part of a healthy life. We know that training effects can improve physical performance, but for high-level athletes, whose performance is measured in seconds or milliseconds, maximum endogenous balance is needed. Conscripts or military servicemen must be able to produce a high level of power in life-threatening situations, similar to the efforts of top athletes. In our studies, we were unable to show that vitamin D levels affect physical performance. These results could be related to our small sample size or might have resulted from suboptimal physical performance tests. However, we conclude that there is no clear effect of vitamin D on physical performance in young male conscripts. Based on the findings in this thesis, we can state that a high rate of vitamin D deficiency occurs in non-supplemented groups. Also, it is the case that a low supplementation dose of up to 1200 IU seems to have a limited effect in increasing serum 25(OH)D levels in humans. This leads us to the next issue – prevention of future public health problems. We should focus on the younger generation to improve vitamin D status through supplementation in different forms. Food fortification has shown very promising results in the Nordic countries. The main problem with fortification is the change in diets, with a recent decrease in milk and milk product consumption. We should therefore try to find new supplementation and fortification methods. Public health specialists, together with food manufacturers, should find solutions to fortify food products that are more popular among the younger generation. Based on current studies, the supplementation minimum in adults is 1200 IU, and even supplementation with up to 4000 IU can be used in cases of severe deficiency and for wintertime supplementation. We also suggest regular measurement of vitamin D to identify the most appropriate supplementation dosage, at least in the winter- and springtime. Natural sources of vitamin D, especially in

the summertime, are of course also recommended. Foremost, we need more recreational outdoor activities. During the first study, 1200 IU was the maximum supplementation dose. This has been increased in Estonia to 4000 IU at present. According to some public health guidelines, we still find a maximum supplementation recommendation of 800 IU, which seems to be too low based on our findings. New supplementation standards should be recommended by public health authorities in Estonia.

Future studies are needed to illuminate the negative influence of long-term vitamin D deficiency among the young population. Additionally, there needs to be a focused effort on promoting life-long prevention of vitamin D deficiency. Both these goals are related to general public health and should be a part of Estonian health care programs.

7. CONCLUSIONS

Study I. (Rips et al., 2023) Vitamin D deficiency and severe deficiency during winter and spring time is very common among conscripts. Sufficient levels (> 75 nmol/L) of serum 25(OH)D are reported only in 23% of conscripts in summertime. However, severe deficiency of vitamin D has no negative effect on physical performance during military service. PTH- and Ca blood serum levels were within normal ranges during the study.

Study II. (Rips et al., 2022) Wintertime vitamin D3 supplementation with 1200 IU results in fewer conscripts with critically low blood serum (25(OH)D) levels during the winter- and springtime compared to a placebo group. However, supplementation does not raise blood serum 25(OH)D to sufficient levels (> 75 nmol/L). Furthermore, supplementation has no effect on physical performance in the form of the hand grip strength test. No significant differences in the PTH, Ca, i-Ca, testosterone and cortisol blood serum levels were found between the study groups at any time point.

Study III. (Rips et al., 2024) A 10-month vitamin D supplementation with 4000 IU decreased the incidence of vitamin D deficiency (< 75 nmol/L) in young male army conscripts during winter- and springtime but had no effect on physical performance based on the APFT and hand grip strength tests compared to 600 IU supplementation.

No significant differences in the PTH, Ca and i-Ca blood serum levels were found between the study groups. However, a significant over-time differences of PTH, Ca and i-Ca blood serum values were found within the study groups, but within normative values. No significant difference in either group at any time point were revealed in terms of BMI.

Overall conclusion. There is high risk of vitamin D deficiency or severe deficiency during winter- and springtime without vitamin D supplementation. In conscripts, it is shown that supplementation with 600 IU has no effect and 1200 IU has minimal effect in keeping blood serum 25(OH)D at baseline levels compared to 4000 IU. Supplementation of vitamin D with 600 IU, 1200 IU, and 4000 IU has no positive effect on physical performance. However, vitamin D deficiency or severe deficiency have no negative effect on physical performance in terms of the APFT and hand grip strength test. Also, despite wide ranges in vitamin D levels in the studies, no effects on PTH, Ca, i-Ca, testosterone, cortisol blood serum levels outside normative values were found.

8. REFERENCES

Allison, R. J., Close, G. L., Farooq, A., Riding, N. R., Salah, O., Hamilton, B., & Wilson, M. G. (2015). Severely vitamin D-deficient athletes present smaller hearts than sufficient athletes. *European Journal of Preventive Cardiology*, *22*(4), 535–542. https://doi.org/10.1177/2047487313518473

Alonso, N., Zelzer, S., Eibinger, G., & Herrmann, M. (2023). Vitamin D metabolites: Analytical challenges and clinical relevance. *Calcified Tissue International*, *112*(2), 158–177. https://doi.org/10.1007/s00223-022-00961-5

Amrein, K., Scherkl, M., Hoffmann, M., Neuwersch-Sommeregger, S., Köstenberger, M., Tmava Berisha, A., Martucci, G., Pilz, S., & Malle, O. (2020). Vitamin D deficiency 2.0: An update on the current status worldwide. *European Journal of Clinical Nutrition*, *74*(11), 1498–1513. https://doi.org/10.1038/s41430-020-0558-y

Armstrong, R. A., Davey, T., Allsopp, A. J., Lanham-New, S. A., Oduoza, U., Cooper, J. A., Montgomery, H. E., & Fallowfield, J. L. (2020). Low serum 25-hydroxyvitamin D status in the pathogenesis of stress fractures in military personnel: An evidenced link to support injury risk management. *PloS One*, *15*(3), e0229638. https://doi.org/10.1371/journal.pone.0229638

Army Basic Training PFT | Military.com. (2024). Retrieved 11th January 2024, from https://www.military.com/military-fitness/army-fitness-requirements/army-basic-training-pft

Aydın, C. G., Dinçel, Y. M., Arıkan, Y., Taş, S. K., & Deniz, S. (2019). The effects of indoor and outdoor sports participation and seasonal changes on vitamin D levels in athletes. *SAGE Open Medicine*, *7*, 2050312119837480. https://doi.org/10.1177/2050312119837480

Bischoff-Ferrari, H. A., Giovannucci, E., Willett, W. C., Dietrich, T., & Dawson-Hughes, B. (2006). Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. *The American Journal of Clinical Nutrition*, *84*(1), 18–28. https://doi.org/10.1093/ajcn/84.1.18

Bohannon, R. W. (2015). Muscle strength: Clinical and prognostic value of hand-grip dynamometry. *Current Opinion in Clinical Nutrition and Metabolic Care*, *18*(5), 465–470. https://doi.org/10.1097/MCO.0000000000000202

Brock, K., Huang, W.-Y., Fraser, D. R., Ke, L., Tseng, M., Stolzenberg-Solomon, R., Peters, U., Ahn, J., Purdue, M., Mason, R. S., McCarty, C., Ziegler, R. G., & Graubard, B. (2010). Low vitamin D status is associated with physical inactivity, obesity and low vitamin D intake in a large US sample of healthy middle-aged men and women. *The Journal of Steroid Biochemistry and Molecular Biology*, *121*(1–2), 462–466. https://doi.org/10.1016/j.jsbmb.2010.03.091

Burdukiewicz, A., Pietraszewska, J., Andrzejewska, J., Chromik, K., & Stachoń, A. (2020). Asymmetry of musculature and hand grip strength in bodybuilders and martial artists. *International Journal of Environmental Research and Public Health*, *17*(13), 4695. https://doi.org/10.3390/ijerph17134695

Calvo, M. S., & Whiting, S. J. (2013). Survey of current vitamin D food fortification practices in the United States and Canada. *The Journal of Steroid Biochemistry and Molecular Biology*, *136*, 211–213. https://doi.org/10.1016/j.jsbmb.2012.09.034

Calvo, M. S., Whiting, S. J., & Barton, C. N. (2005). Vitamin D intake: A global perspective of current status. *The Journal of Nutrition*, *135*(2), 310–316. https://doi.org/10.1093/jn/135.2.310

Cardwell, G., Bornman, J. F., James, A. P., & Black, L. J. (2018). A Review of mushrooms as a potential source of dietary vitamin D. *Nutrients*, *10*(10), 1498. https://doi.org/10.3390/nu10101498

Carswell, A. T., Oliver, S. J., Wentz, L. M., Kashi, D. S., Roberts, R., Tang, J. C. Y., Izard, R. M., Jackson, S., Allan, D., Rhodes, L. E., Fraser, W. D., Greeves, J. P., & Walsh, N. P. (2018). Influence of vitamin D supplementation by sunlight or oral D3 on exercise performance. *Medicine and Science in Sports and Exercise*, *50*(12), 2555–2564. https://doi.org/10.1249/MSS.0000000000001721

Carmeliet, G., Dermauw, V., Bouillon, R. (2015) Vitamin D signaling in calcium and bone homeostasis: a delicate balance. *Best Pract Res Clin Endocrinol Metab.* 29(4):621–31. https://doi.org/10.1016/j.beem.2015.06.001

Cashman, K. D., Fitzgerald, A. P., Kiely, M., & Seamans, K. M. (2011). A systematic review and meta-regression analysis of the vitamin D intake-serum 25-hydroxy-vitamin D relationship to inform European recommendations. *The British Journal of Nutrition*, *106*(11), 1638–1648. https://doi.org/10.1017/S0007114511005058

Cashman, K. D., & Kiely, M. (2014). Recommended dietary intakes for vitamin D: Where do they come from, what do they achieve and how can we meet them? *Journal of Human Nutrition and Dietetics: The Official Journal of the British Dietetic Association*, *27*(5), 434–442. https://doi.org/10.1111/jhn.12226

Casto, K. V., & Edwards, D. A. (2016). Testosterone, cortisol, and human competition. *Hormones and Behavior*, *82*, 21–37. https://doi.org/10.1016/j.yhbeh.2016.04.004

Chen, C., Zhai, H., Cheng, J., Weng, P., Chen, Y., Li, Q., Wang, C., Xia, F., Wang, N., & Lu, Y. (2019). Causal link between vitamin D and total testosterone in men: A Mendelian randomization analysis. *The Journal of Clinical Endocrinology and Metabolism*, *104*(8), 3148–3156. https://doi.org/10.1210/jc.2018-01874

Chen, C.-Y., McGee, C. W., Rich, T. L., Prudente, C. N., & Gillick, B. T. (2018). Reference values of intrinsic muscle strength of the hand of adolescents and young adults. *Journal of Hand Therapy: Official Journal of the American Society of Hand Therapists*, *31*(3), 348–356. https://doi.org/10.1016/j.jht.2017.05.012

Christopher, J. J., Schindler, J., Villa, J., Hussey, E., Ramsay, J., & Brown, S. A. T. (2019). Holding on tight: Relationship between grip strength and marksmanship stability. *Proceedings of the Human Factors and Ergonomics Society Annual Meeting*, *63*(1), 2156–2160. https://doi.org/10.1177/1071181319631104

de Gruijl, F. R. (2011). Sufficient vitamin D from casual sun exposure? *Photochemistry and Photobiology*, *87*(3), 598–601. https://doi.org/10.1111/j.1751-1097.2011.00918.x

DeLuca, H. F. (2004). Overview of general physiologic features and functions of vitamin D. *The American Journal of Clinical Nutrition*, *80*(6 Suppl), 1689S–96S. https://doi.org/10.1093/ajcn/80.6.1689S

Dietary reference values for vitamin D | EFSA. (2016, October 28). https://www.efsa.europa.eu/en/efsajournal/pub/4547

Dodds, R. M., Syddall, H. E., Cooper, R., Benzeval, M., Deary, I. J., Dennison, E. M., Der, G., Gale, C. R., Inskip, H. M., Jagger, C., Kirkwood, T. B., Lawlor, D. A., Robinson, S. M., Starr, J. M., Steptoe, A., Tilling, K., Kuh, D., Cooper, C., & Sayer, A. A. (2014). Grip strength across the life course: Normative data from twelve British studies. *PloS One*, *9*(12), e113637. https://doi.org/10.1371/journal.pone.0113637

Dodds, R. M., Syddall, H. E., Cooper, R., Kuh, D., Cooper, C., & Sayer, A. A. (2016). Global variation in grip strength: A systematic review and meta-analysis of normative data. *Age and Ageing*, *45*(2), 209–216. https://doi.org/10.1093/ageing/afv192

Drake, T. M., & Gupta, V. (2024). Calcium. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK557683/

Duclos, M., Gouarne, C., & Bonnemaison, D. (2003). Acute and chronic effects of exercise on tissue sensitivity to glucocorticoids. *Journal of Applied Physiology (Bethesda, Md.: 1985)*, *94*(3), 869–875. https://doi.org/10.1152/japplphysiol.00108.2002

Fagnant, H. S., Lutz, L. J., Nakayama, A. T., Gaffney-Stomberg, E., McClung, J. P., & Karl, J. P. (2022). Breakfast skipping is associated with vitamin D deficiency among young adults entering initial military training. *Journal of the Academy of Nutrition and Dietetics*, *122*(6), 1114-1128.e1. https://doi.org/10.1016/j.jand.2021.09.016

Fairbairn, K. A., Ceelen, I. J. M., Skeaff, C. M., Cameron, C. M., & Perry, T. L. (2018). Vitamin D3 supplementation does not improve sprint performance in professional rugby players: A randomized, placebo-controlled, double-blind intervention study. *International Journal of Sport Nutrition and Exercise Metabolism*, *28*(1), 1–9. https://doi.org/10.1123/ijsnem.2017-0157

Fogleman, S. A., Janney, C., Cialdella-Kam, L., & Flint, J. H. (2022). Vitamin D deficiency in the military: It's time to act! *Military Medicine*, *187*(5–6), 144–148. https://doi.org/10.1093/milmed/usab402

Funderburk, L. K., Daigle, K., & Arsenault, J. E. (2015). Vitamin D status among overweight and obese soldiers. *Military Medicine*, *180*(2), 237–240. https://doi.org/10.7205/MILMED-D-14-00041

Gaffney-Stomberg, E., Hughes, J. M., Guerriere, K. I., Staab, J. S., Cable, S. J., Bouxsein, M. L., & McClung, J. P. (2022). Once daily calcium (1000 mg) and vitamin D (1000 IU) supplementation during military training prevents increases in biochemical markers of bone resorption but does not affect tibial microarchitecture in Army recruits. *Bone*, *155*, 116269. https://doi.org/10.1016/j.bone.2021.116269

Gaffney-Stomberg, E., Nakayama, A. T., Guerriere, K. I., Lutz, L. J., Walker, L. A., Staab, J. S., Scott, J. M., Gasier, H. G., & McClung, J. P. (2019). Calcium and vitamin D supplementation and bone health in Marine recruits: Effect of season. *Bone*, *123*, 224–233. https://doi.org/10.1016/j.bone.2019.03.021

Geiker, N. R. W., Hansen, M., Jakobsen, J., Kristensen, M., Larsen, R., Jørgensen, N. R., Hansen, B. S., & Bügel, S. (2017). Vitamin D status and muscle function among adolescent and young swimmers. *International Journal of Sport Nutrition and Exercise Metabolism*, *27*(5), 399–407. https://doi.org/10.1123/ijsnem.2016-0248

Girgis, C. M., Clifton-Bligh, R. J., Hamrick, M. W., Holick, M. F., & Gunton, J. E. (2013). The roles of vitamin D in skeletal muscle: Form, function, and metabolism. *Endocrine Reviews*, *34*(1), 33–83. https://doi.org/10.1210/er.2012-1012

Giustina, A., Adler, R. A., Binkley, N., Bollerslev, J., Bouillon, R., Dawson-Hughes, B., Ebeling, P. R., Feldman, D., Formenti, A. M., Lazaretti-Castro, M., Marcocci, C., Rizzoli, R., Sempos, C. T., & Bilezikian, J. P. (2020). Consensus statement from 2nd International Conference on Controversies in Vitamin D. *Reviews in Endocrine & Metabolic Disorders*, *21*(1), 89–116. https://doi.org/10.1007/s11154-019-09532-w

Gonçalves, M., Marson, R., Fortes, M., Neves, E., Neto, G., & Novaes, J. (2018). The relationship between handgrip strength and total muscle strength in the Brazilian army military personnel. *Medicina Dello Sport; Rivista Di Fisiopatologia Dello Sport*, *71*, 461–473. https://doi.org/10.23736/S0025-7826.18.03117-4

Glenville, J. Pharmacokinetics of vitamin D toxicity. (2008) *Am J Clin Nutr. 88,582S-586S.* https://doi.org/10.1093/ajcn/88.2.582S

Granlund, L., Norberg, M., Ramnemark, A., Andersson, C., Lindkvist, M., & Fhärm, E. (2018). Vitamin D is associated with lower limb muscle strength and grip strength in

Middle Eastern- and African-born immigrants in Sweden. *Nutrition Research (New York, N.Y.)*, *59*, 29–35. https://doi.org/10.1016/j.nutres.2018.07.009

Halliday, T. M., Peterson, N. J., Thomas, J. J., Kleppinger, K., Hollis, B. W., & Larson-Meyer, D. E. (2011). Vitamin D status relative to diet, lifestyle, injury, and illness in college athletes. *Medicine and Science in Sports and Exercise*, *43*(2), 335–343. https://doi.org/10.1249/MSS.0b013e3181eb9d4d

Handelsman, D. J., Hirschberg, A. L., & Bermon, S. (2018). Circulating testosterone as the hormonal basis of sex differences in athletic performance. *Endocrine Reviews*, *39*(5), 803–829. https://doi.org/10.1210/er.2018-00020

Harrison, S. E., Oliver, S. J., Kashi, D. S., Carswell, A. T., Edwards, J. P., Wentz, L. M., Roberts, R., Tang, J. C. Y., Izard, R. M., Jackson, S., Allan, D., Rhodes, L. E., Fraser, W. D., Greeves, J. P., & Walsh, N. P. (2021). Influence of vitamin D supplementation by simulated sunlight or oral D3 on respiratory infection during military training. *Medicine and Science in Sports and Exercise*, *53*(7), 1505–1516. https://doi.org/10.1249/MSS.0000000000002604

Heileson, J. L., McGowen, J. M., Moris, J. M., Chapman-Lopez, T. J., Torres, R., Funderburk, L. K., & Forsse, J. S. (2022). Body composition, eicosapentaenoic acid, and vitamin D are associated with Army Combat Fitness Test performance. *Journal of the International Society of Sports Nutrition*, *19*(1), 349–365. https://doi.org/10.1080/15502783.2022.2094717

Henriques, M., Rodrigues, D., Sacadura-Leite, E., Viegas, S., & Serranheira, F. (2022). Vitamin D status in the active duty navy military personnel: Protocol for a systematic review. *BMJ Open*, *12*(5), e060876. https://doi.org/10.1136/bmjopen-2022-060876

Henriques, M., Rodrigues, D., Viegas, S., Serranheira, F., & Sacadura-Leite, E. (2023). Vitamin D status in active duty navy military personnel: A systematic review. *Occupational and Environmental Medicine*, *80*(6), 353–360. https://doi.org/10.1136/oemed-2022-108710

Herrmann, M. (2023). Assessing vitamin D metabolism – four decades of experience. *Clinical Chemistry and Laboratory Medicine (CCLM)*, *61*(5), 880–894. https://doi.org/10.1515/cclm-2022-1267

Holick, M. F. (2003). Vitamin D: A millenium perspective. *Journal of Cellular Biochemistry*, *88*(2), 296–307. https://doi.org/10.1002/jcb.10338

Holick, M. F. (2004). Vitamin D: Importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. *The American Journal of Clinical Nutrition*, *79*(3), 362–371. https://doi.org/10.1093/ajcn/79.3.362

Holick, M. F. (2009). Vitamin D status: Measurement, interpretation and clinical application. *Annals of Epidemiology*, *19*(2), 73–78. https://doi.org/10.1016/j.annepidem.2007.12.001

Holick, M. F. (2011). Vitamin D: A d-lightful solution for health. *Journal of Investigative Medicine: The Official Publication of the American Federation for Clinical Research*, *59*(6), 872–880. https://doi.org/10.2310/JIM.0b013e318214ea2d

Holick, M. F., Binkley, N. C., Bischoff-Ferrari, H. A., Gordon, C. M., Hanley, D. A., Heaney, R. P., Murad, M. H., Weaver, C. M., & Endocrine Society. (2011). Evaluation, treatment, and prevention of vitamin D deficiency: An Endocrine Society clinical practice guideline. *The Journal of Clinical Endocrinology and Metabolism*, *96*(7), 1911–1930. https://doi.org/10.1210/jc.2011-0385

Holick, M. F., Tian, X. Q., & Allen, M. (1995). Evolutionary importance for the membrane enhancement of the production of vitamin D3 in the skin of poikilothermic

animals. *Proceedings of the National Academy of Sciences of the United States of America*, *92*(8), 3124–3126. https://doi.org/10.1073/pnas.92.8.3124

Huerta Ojeda, Á., Fontecilla Díaz, B., Yeomans Cabrera, M. M., & Jerez-Mayorga, D. (2021). Grip power test: A new valid and reliable method for assessing muscle power in healthy adolescents. *PLoS ONE*, *16*(10), e0258720. https://doi.org/10.1371/journal.pone.0258720

Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. (2011). *Dietary Reference Intakes for Calcium and Vitamin D* (A. C. Ross, C. L. Taylor, A. L. Yaktine, & H. B. Del Valle, Eds.). National Academies Press (US). http://www.ncbi.nlm.nih.gov/books/NBK56070/

Jääskeläinen, T., Itkonen, S. T., Lundqvist, A., Erkkola, M., Koskela, T., Lakkala, K., Dowling, K. G., Hull, G. L., Kröger, H., Karppinen, J., Kyllönen, E., Härkänen, T., Cashman, K. D., Männistö, S., & Lamberg-Allardt, C. (2017). The positive impact of general vitamin D food fortification policy on vitamin D status in a representative adult Finnish population: Evidence from an 11-y follow-up based on standardized 25-hydroxyvitamin D data. *The American Journal of Clinical Nutrition*, *105*(6), 1512–1520. https://doi.org/10.3945/ajcn.116.151415

Jäpelt, R. B., & Jakobsen, J. (2013). Vitamin D in plants: A review of occurrence, analysis, and biosynthesis. *Frontiers in Plant Science*, *4*, 136. https://doi.org/10.3389/fpls.2013.00136

Jenkinson, C., Desai, R., Slominski, A. T., Tuckey, R. C., Hewison, M., & Handelsman, D. J. (2021). Simultaneous measurement of 13 circulating vitamin D3 and D2 mono and dihydroxy metabolites using liquid chromatography mass spectrometry. *Clinical Chemistry and Laboratory Medicine (CCLM)*, *59*(10), 1642–1652. https://doi.org/10.1515/cclm-2021-0441

Khundmiri, S. J., Murray, R. D., & Lederer, E. (2016). PTH and vitamin D. *Comprehensive Physiology*, *6*(2), 561–601. https://doi.org/10.1002/cphy.c140071

Knapik, J. J., Farina, E. K., Fulgoni, V. L., & Lieberman, H. R. (2021). Clinically-diagnosed vitamin deficiencies and disorders in the entire United States military population, 1997-2015. *Nutrition Journal*, *20*(1), 55. https://doi.org/10.1186/s12937-021-00708-2

Koundourakis, N. E., Androulakis, N. E., Malliaraki, N., & Margioris, A. N. (2014). Vitamin D and exercise performance in professional soccer players. *PLOS ONE*, *9*(7), e101659. https://doi.org/10.1371/journal.pone.0101659

Kraemer, W. J., Ratamess, N. A., Hymer, W. C., Nindl, B. C., & Fragala, M. S. (2020). Growth hormone(s), testosterone, insulin-like growth factors, and cortisol: Roles and integration for cellular development and growth with exercise. *Frontiers in Endocrinology*, *11*, 33. https://doi.org/10.3389/fendo.2020.00033

Książek, A., Dziubek, W., Pietraszewska, J., & Słowińska-Lisowska, M. (2018). Relationship between 25(OH)D levels and athletic performance in elite Polish judoists. *Biology of Sport*, *35*(2), 191–196. https://doi.org/10.5114/biolsport.2018.74195

Kull, M., Kallikorm, R., Tamm, A., & Lember, M. (2009). Seasonal variance of 25-(OH) vitamin D in the general population of Estonia, a Northern European country. *BMC Public Health*, *9*, 22. https://doi.org/10.1186/1471-2458-9-22

Kuo, Y.-T., Kuo, L.-K., Chen, C.-W., Yuan, K.-C., Fu, C.-H., Chiu, C.-T., Yeh, Y.-C., Liu, J.-H., & Shih, M.-C. (2022). Score-based prediction model for severe vitamin D deficiency in patients with critical illness: Development and validation. *Critical Care (London, England)*, *26*(1), 394. https://doi.org/10.1186/s13054-022-04274-9

Laaksi, I., Ruohola, J.-P., Mattila, V., Auvinen, A., Ylikomi, T., & Pihlajamäki, H. (2010). Vitamin D supplementation for the prevention of acute respiratory tract infection: A randomized, double-blinded trial among young Finnish men. *The Journal of Infectious Diseases*, *202*(5), 809–814. https://doi.org/10.1086/654881

Laaksi, I., Ruohola, J.-P., Tuohimaa, P., Auvinen, A., Haataja, R., Pihlajamäki, H., & Ylikomi, T. (2007). An association of serum vitamin D concentrations < 40 nmol/L with acute respiratory tract infection in young Finnish men. *The American Journal of Clinical Nutrition*, *86*(3), 714–717. https://doi.org/10.1093/ajcn/86.3.714

Laaksi, I. T., Ruohola, J.-P. S., Ylikomi, T. J., Auvinen, A., Haataja, R. I., Pihlajamäki, H. K., & Tuohimaa, P. J. (2006). Vitamin D fortification as public health policy: Significant improvement in vitamin D status in young Finnish men. *European Journal of Clinical Nutrition*, *60*(8), 1035–1038. https://doi.org/10.1038/sj.ejcn.1602414

Lamberg-Allardt, C. (2006). Vitamin D in foods and as supplements. *Progress in Biophysics and Molecular Biology*, *92*(1), 33–38. https://doi.org/10.1016/j.pbiomolbio.2006.02.017

Lamberg-Allardt, C., Brustad, M., Meyer, H. E., & Steingrimsdottir, L. (2013). Vitamin D – a systematic literature review for the 5th edition of the Nordic Nutrition Recommendations. *Food & Nutrition Research*, *57*. https://doi.org/10.3402/fnr.v57i0.22671

Lamberg-Allardt, C. J., Outila, T. A., Kärkkainen, M. U., Rita, H. J., & Valsta, L. M. (2001). Vitamin D deficiency and bone health in healthy adults in Finland: Could this be a concern in other parts of Europe? *Journal of Bone and Mineral Research: The Official Journal of the American Society for Bone and Mineral Research*, *16*(11), 2066–2073. https://doi.org/10.1359/jbmr.2001.16.11.2066

Lips, P. (2006). Vitamin D physiology. *Progress in Biophysics and Molecular Biology*, *92*(1), 4–8. https://doi.org/10.1016/j.pbiomolbio.2006.02.016

Lips, P., Cashman, K. D., Lamberg-Allardt, C., Bischoff-Ferrari, H. A., Obermayer-Pietsch, B., Bianchi, M. L., Stepan, J., El-Hajj Fuleihan, G., & Bouillon, R. (2019). Current vitamin D status in European and Middle East countries and strategies to prevent vitamin D deficiency: A position statement of the European Calcified Tissue Society. *European Journal of Endocrinology*, *180*(4), P23–P54. https://doi.org/10.1530/EJE-18-0736

Lips, P., Hosking, D., Lippuner, K., Norquist, J. M., Wehren, L., Maalouf, G., Ragi-Eis, S., & Chandler, J. (2006). The prevalence of vitamin D inadequacy amongst women with osteoporosis: An international epidemiological investigation. *Journal of Internal Medicine*, *260*(3), 245–254. https://doi.org/10.1111/j.1365-2796.2006.01685.x

Lofrese, J. J., Basit, H., & Lappin, S. L. (2024). Physiology, Parathyroid. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK482510/

Mason, R. S., Rybchyn, M. S., Abboud, M., Brennan-Speranza, T. C., & Fraser, D. R. (2019). The role of skeletal muscle in maintaining vitamin D status in winter. *Current Developments in Nutrition*, *3*(10), nzz087. https://doi.org/10.1093/cdn/nzz087

McCarthy, M. S., Elshaw, E. B., Szekely, B. M., & Raju, D. (2019). A prospective cohort study of vitamin D supplementation in AD soldiers: Preliminary findings. *Military Medicine*, *184*(Suppl 1), 498–505. https://doi.org/10.1093/milmed/usy393

McCollum, E. V., Simmonds, N., Becker, J. E., & Shipley, P. G. (1922). Studies on experimental rickets. *Journal of Biological Chemistry*, *53*(2), 293–312. https://doi.org/10.1016/S0021-9258(18)85783-0

Menon, A. S., Anayath, S., Garg, M. K., Kapoor, R., & Pisharody, I. (2020). The effect of vitamin D supplementation on cardiorespiratory fitness and muscle strength

in male adults undergoing basic military training. *Medical Journal, Armed Forces India*, *76*(1), 71–76. https://doi.org/10.1016/j.mjafi.2018.12.004

Mielgo-Ayuso, J., Calleja-González, J., Urdampilleta, A., León-Guereño, P., Córdova, A., Caballero-García, A., & Fernandez-Lázaro, D. (2018). Effects of vitamin D supplementation on haematological values and muscle recovery in elite male traditional rowers. *Nutrients*, *10*(12), 1968. https://doi.org/10.3390/nu10121968

Montenegro, K. R., Cruzat, V., Carlessi, R., & Newsholme, P. (2019). Mechanisms of vitamin D action in skeletal muscle. *Nutrition Research Reviews*, *32*(2), 192–204. https://doi.org/10.1017/S0954422419000064

Nimptsch, K., Platz, E. A., Willett, W. C., & Giovannucci, E. (2012). Association between plasma 25-OH vitamin D and testosterone levels in men. *Clinical Endocrinology*, *77*(1), 106–112. https://doi.org/10.1111/j.1365-2265.2012.04332.x

Ööpik, V., Timpmann, S., Rips, L., Olveti, I., Kõiv, K., Mooses, M., Mölder, H., Varblane, A., Lille, H.-R., & Gapeyeva, H. (2017). Anabolic adaptations occur in conscripts during basic military training despite high prevalence of vitamin D deficiency and decrease in iron status. *Military Medicine*, *182*(3), e1810–e1818. https://doi.org/10.7205/MILMED-D-16-00113

Orysiak, J., Mazur-Rozycka, J., Fitzgerald, J., Starczewski, M., Malczewska-Lenczowska, J., & Busko, K. (2018). Vitamin D status and its relation to exercise performance and iron status in young ice hockey players. *PLOS ONE*, *13*(4), e0195284. https://doi.org/10.1371/journal.pone.0195284

Płudowski, P., Karczmarewicz, E., Bayer, M., Carter, G., Chlebna-Sokół, D., Czech-Kowalska, J., Dębski, R., Decsi, T., Dobrzańska, A., Franek, E., Głuszko, P., Grant, W. B., Holick, M. F., Yankovskaya, L., Konstantynowicz, J., Książyk, J. B., Księżopolska-Orłowska, K., Lewiński, A., Litwin, M., … Żmijewski, M. A. (2013). Practical guidelines for the supplementation of vitamin D and the treatment of deficits in Central Europe—Recommended vitamin D intakes in the general population and groups at risk of vitamin D deficiency. *Endokrynologia Polska*, *64*(4), 319–327. https://doi.org/10.5603/ep.2013.0012

Płudowski, P., Kos-Kudła, B., Walczak, M., Fal, A., Zozulińska-Ziółkiewicz, D., Sieroszewski, P., Peregud-Pogorzelski, J., Lauterbach, R., Targowski, T., Lewiński, A., Spaczyński, R., Wielgoś, M., Pinkas, J., Jackowska, T., Helwich, E., Mazur, A., Ruchała, M., Zygmunt, A., Szalecki, M., … Misiorowski, W. (2023). Guidelines for preventing and treating vitamin D deficiency: A 2023 update in Poland. *Nutrients*, *15*(3), 695. https://doi.org/10.3390/nu15030695

Potter, A. W., Soto, L. D., & Friedl, K. E. (2022). Body composition of extreme performers in the US Marine Corps. *BMJ Military Health*, e002189. https://doi.org/10.1136/military-2022-002189

Rajab, H. A. (2022). The effect of vitamin D level on parathyroid hormone and alkaline phosphatase. *Diagnostics (Basel, Switzerland)*, *12*(11), 2828. https://doi.org/10.3390/diagnostics12112828

Rips, L., Toom, A., Kuik, R., Varblane, A., Mölder, H., Tammaru, M., Kull, M., Ööpik, V., Kartus, J.-T., Gapeyeva, H., & Rahu, M. (2022). Seven-month wintertime supplementation of 1200 IU vitamin D has no effect on hand grip strength in young, physically active males: A randomized, controlled study. *Journal of the International Society of Sports Nutrition*, *19*(1), 437–454. https://doi.org/10.1080/15502783.2022.2100718

Rips, L., Toom, A., Kuik, R., Varblane, A., Mölder, H., Kull, M., Kartus, J.-T., Gapeyeva, H., & Rahu, M. (2023). Severe deficiency of vitamin D has no negative effect on

physical performance during military training. *The Journal of Sports Medicine and Physical Fitness*, *63*(2), 329–338. https://doi.org/10.23736/S0022-4707.22.14123-X

Rips, L., Toom, A., Kuik, R., Varblane, A., Mölder, H., Kibur, R., Laidvere, M., Kull, M., Kartus, J.-T., Gapeyeva, H., & Rahu, M. (2024). High dose vitamin D supplementation decreases the risk of deficiency in male conscripts, but has no effect on physical performance – a randomized study. *Journal of Experimental Orthopaedics*, e12023. https://doi.org/10.1002/jeo2.12023.

Savolainen, L., Timpmann, S., Mooses, M., Mäestu, E., Medijainen, L., Tõnutare, L., Ross, F., Lellsaar, M., Unt, E., & Ööpik, V. (2021). Vitamin D supplementation does not enhance resistance training-induced gains in muscle strength and lean body mass in vitamin D deficient young men. *European Journal of Applied Physiology*, *121*(7), 2077–2090. https://doi.org/10.1007/s00421-021-04674-9

Schaad, K. A., Bukhari, A. S., Brooks, D. I., Kocher, J. D., & Barringer, N. D. (2019). The relationship between vitamin D status and depression in a tactical athlete population. *Journal of the International Society of Sports Nutrition*, *16*(1), 40. https://doi.org/10.1186/s12970-019-0308-5

Scott, J. M., Kazman, J. B., Palmer, J., McClung, J. P., Gaffney-Stomberg, E., & Gasier, H. G. (2019). Effects of vitamin D supplementation on salivary immune responses during Marine Corps basic training. *Scandinavian Journal of Medicine & Science in Sports*, *29*(9), 1322–1330. https://doi.org/10.1111/sms.13467

Shen, M., Li, Z., Lv, D., Yang, G., Wu, R., Pan, J., Wang, S., Li, Y., & Xu, S. (2020). Seasonal variation and correlation analysis of vitamin D and parathyroid hormone in Hangzhou, Southeast China. *Journal of Cellular and Molecular Medicine*, *24*(13), 7370–7377. https://doi.org/10.1111/jcmm.15330

Sinha, A., Hollingsworth, K. G., Ball, S., & Cheetham, T. (2013). Improving the vitamin D status of vitamin D deficient adults is associated with improved mitochondrial oxidative function in skeletal muscle. *The Journal of Clinical Endocrinology and Metabolism*, *98*(3), E509–513. https://doi.org/10.1210/jc.2012-3592

Sivakumar, G., Koziarz, A., & Farrokhyar, F. (2019). Vitamin D supplementation in military personnel: A systematic review of randomized controlled trials. *Sports Health*, *11*(5), 425–431. https://doi.org/10.1177/1941738119857717

Skalska, M., Nikolaidis, P. T., Knechtle, B., Rosemann, T. J., Radzimiński, Ł., Jastrzębska, J., Kaczmarczyk, M., Myśliwiec, A., Dragos, P., López-Sánchez, G. F., & Jastrzębski, Z. (2019). Vitamin D supplementation and physical activity of young soccer players during high-intensity training. *Nutrients*, *11*(2), Article 2. https://doi.org/10.3390/nu11020349

Spiro, A., & Buttriss, J. L. (2014). Vitamin D: An overview of vitamin D status and intake in Europe. *Nutrition Bulletin*, *39*(4), 322–350. https://doi.org/10.1111/nbu.12108

Stockton, K. A., Mengersen, K., Paratz, J. D., Kandiah, D., & Bennell, K. L. (2011). Effect of vitamin D supplementation on muscle strength: A systematic review and meta-analysis. *Osteoporosis International: A Journal Established as Result of Cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*, *22*(3), 859–871. https://doi.org/10.1007/s00198-010-1407-y

Todd, J. J., McSorley, E. M., Pourshahidi, L. K., Madigan, S. M., Laird, E., Healy, M., & Magee, P. J. (2017). Vitamin D3 supplementation using an oral spray solution resolves deficiency but has no effect on VO2 max in Gaelic footballers: Results from a randomised, double-blind, placebo-controlled trial. *European Journal of Nutrition*, *56*(4), 1577–1587. https://doi.org/10.1007/s00394-016-1202-4

United States Army Physical Fitness Test. (2024). In Wikipedia. https://en.wikipedia.org/w/index.php?title=United_States_Army_Physical_Fitness_Test&oldid=1193131570

Välimäki, V.-V., Alfthan, H., Lehmuskallio, E., Löyttyniemi, E., Sahi, T., Stenman, U.-H., Suominen, H., & Välimäki, M. J. (2004). Vitamin D status as a determinant of peak bone mass in young Finnish men. *The Journal of Clinical Endocrinology and Metabolism*, *89*(1), 76–80. https://doi.org/10.1210/jc.2003-030817

Wahl, D. A., Cooper, C., Ebeling, P. R., Eggersdorfer, M., Hilger, J., Hoffmann, K., Josse, R., Kanis, J. A., Mithal, A., Pierroz, D. D., Stenmark, J., Stöcklin, E., & Dawson-Hughes, B. (2012). A global representation of vitamin D status in healthy populations. *Archives of Osteoporosis*, *7*, 155–172. https://doi.org/10.1007/s11657-012-0093-0

Wang, Y., Zhu, J., & DeLuca, H. F. (2012). Where is the vitamin D receptor? *Archives of Biochemistry and Biophysics*, *523*(1), 123–133. https://doi.org/10.1016/j.abb.2012.04.001

Wiciński, M., Adamkiewicz, D., Adamkiewicz, M., Śniegocki, M., Podhorecka, M., Szychta, P., & Malinowski, B. (2019). Impact of vitamin D on physical efficiency and exercise performance – a review. *Nutrients*, *11*(11), 2826. https://doi.org/10.3390/nu11112826

Willis, K. S., Peterson, N. J., & Larson-Meyer, D. E. (2008). Should we be concerned about the vitamin D status of athletes? *International Journal of Sport Nutrition and Exercise Metabolism*, *18*(2), 204–224. https://doi.org/10.1123/ijsnem.18.2.204

Windaus, A., & Grundmann, W. (1936). Über die Konstitution des Vitamins D2. II. *Justus Liebigs Annalen Der Chemie*, *524*(1), 295–299. https://doi.org/10.1002/jlac.19365240116

Wintermeyer, E., Ihle, C., Ehnert, S., Stöckle, U., Ochs, G., de Zwart, P., Flesch, I., Bahrs, C., & Nussler, A. K. (2016). Crucial role of vitamin D in the musculoskeletal system. *Nutrients*, *8*(6), 319. https://doi.org/10.3390/nu8060319

Wolters, M., Intemann, T., Russo, P., Moreno, L. A., Molnár, D., Veidebaum, T., Tornaritis, M., De Henauw, S., Eiben, G., Ahrens, W., & Floegel, A. (2022). 25-Hydroxyvitamin D reference percentiles and the role of their determinants among European children and adolescents. *European Journal of Clinical Nutrition*, *76*(4), 564–573. https://doi.org/10.1038/s41430-021-00985-4

Wrzosek, M., Woźniak, J., & Włodarek, D. (2020). The combination of a diversified intake of carbohydrates and fats and supplementation of vitamin D in a diet does not affect the levels of hormones (testosterone, estradiol, and cortisol) in men practicing strength training for the duration of 12 weeks. *International Journal of Environmental Research and Public Health*, *17*(21), 8057. https://doi.org/10.3390/ijerph17218057

Zeitler, C., Fritz, R., Smekal, G., & Ekmekcioglu, C. (2018). Association between the 25-hydroxyvitamin D status and physical performance in healthy recreational athletes. *International Journal of Environmental Research and Public Health*, *15*(12), 2724. https://doi.org/10.3390/ijerph15122724

Zhang, L., Quan, M., & Cao, Z.-B. (2019). Effect of vitamin D supplementation on upper and lower limb muscle strength and muscle power in athletes: A meta-analysis. *PloS One*, *14*(4), e0215826. https://doi.org/10.1371/journal.pone.0215826

9. SUMMARY IN ESTONIAN

D-vitamiini mõju füüsilisele võimekusele Eesti Kaitseväe ajateenjatel

D-vitamiin defitsiit ja sellega seotud mõjud tervisele ja füüsilisele võimekusele on viimastel aastakümnetel oluliselt suurendanud D-vitamiiniga seotud teadus-uuringute arvu maailmas (Knapik et al., 2021; Menon et al., 2020; Wintermeyer et al., 2016). Avaldatud tööd on näidanud, et D-vitamiinil on oluline mõju inimese muskuloskeletaalsüsteemile, eriti luu metabolismile ning defitsiidi tingimustes tõuseb risk osteopeeniale ja osteoporoosile, luumurdudele, stressmurdudele ning lisaks immunsüsteemi funktsionihäiretele ja lihasvõimekuse langusele (Carswell et al., 2018; Halliday et al., 2011; Holick, 2009, 2011; Holick et al., 2011; Sinha et al., 2013). D-vitamiini defitsiidi risk esineb kõigis vanusegruppides ning tõuseb väga suure füüsilise ja vaimse koormusega seotud tegevusaladel, mille hulka kuulub ka sõjaväeteenistus (Gaffney-Stomberg et al., 2019; Harrison et al., 2021; Sivakumar et al., 2019). Füüsiline võimekus on sõjaväes kriitilise tähtsusega nii väljaõppel kui ka missioonidel. Samas näitavad mitmed uuringud vastukäivaid seoseid füüsilise võimekuse ja D-vitamiini defitsiidi vahel. D-vitamiini positiivset mõju sõjaväelaste füüsilisele võimekusele on leitud siiski vaid vähestel uuringutel. (Carswell et al., 2018; Stockton et al., 2011; Zeitler et al., 2018). Samas paljud uuringud ei ole näidanud seoseid D-vitamiini taseme ja füüsilise võimekuse vahel nii sõjaväelastel kui ka sportlastel (Carswell et al., 2018; Geiker et al., 2017; Heileson et al., 2022; Mason et al., 2019; Menon et al., 2020; Stockton et al., 2011; Zhang et al., 2019).

Eestis ei ole varem uuritud D-vitamiini aastaringseid muutuseid, regulaarset pikaajalist lisamanustamist ning mõjusid füüsilisele võimekusele noortel tervetel meestel kõrge füüsilise aktiivsuse perioodidel. Teostatud on vaid lühiperioodilisi uuringuid täiskasvanutel (Kull et al., 2009) ja sportlastel (Savolainen et al., 2021).

Antud doktoritöö põhieesmärgiks oli määrata Eesti Kaitseväe ajateenijatel ajateenistuse ajal D-vitamini, e. vereseerumi 25(OH)D tasemed aastaringselt ning leida sobivaimad lisamanustamise annused. Kaasnevateks eesmärkideks oli hinnata D-vitamiini defitsiidi esinemisagedus ja D-vitamiini erinevate annuste manustamise mõju füüsilisele võimekusele. Samuti määrati D-vitamiini mõju PTH, Ca, i-Ca, testosterooni ja kortisooli vereseerumi tasemetele ning BMI-le.

Uuringu käigus määrati vereseerumi 25(OH)D sisaldus nii lühiajaliselt talveperioodil kui ka kogu aasta jooksul koos füüsiliste testitega (APFT) ja käe pigistusjõu määramisega nii D-vitamiini suukaudse manustamisega ja ka ilma manustamiseta kokku kolmes uuringus.

I uuring. Esimeses, 10-ne kuulises uuringus Juulist kuni Mai kuuni, osales kokku 88 meessoost ajateenijat. Uuringu jooksul teostati kokku 3 korda APFT test, 4 korda domineeriva käe pigistusjõu test ning 4 korda hinnati vereseerumi 25(OH)D, parathormooni ja kaltsiumi sisaldust. Väga oluline 25(OH)D langus esines talve ja kevadperioodil (31.9 nmol/l Märtsis) võrreldes kesksuve

algnäitajatega (61.8 nmol/l Juulis). Kõige enam esines 25(OH)D kriitilist defitsiiti (<25 nmo/l) kevadel, kokku 36% kõigist uuritavatest. Märtsiks ei leitud ühelgil uuritaval soovituslikku D-vitamiini taset (>75 nmol/l). Parathormooni ja kaltsiumi vereseerumi keskmised näitajad varieerusid normi piirides. Vaatamata D-vitamiini defitsiidile ja kriitilisele defitsiidile ei mõjutanud see negatiivselt füüsilise võimekuse näitajatele (APFT) ja domineeriva käe pigistusjõule.

II uuring. Teises, 7 kuulises prospektiivses randomiseeritud kaksikpimedas uuringus osales kokku 53 meesajateenijat. Randomiseerimise käigus jagati uuritavad rühmad kaheks, interventsioonirühm 27 osalejaga, kes manustas 1200 ühiku D vitamiini ja platseeborühm 26 osalejaga, kes manustasid platseebokapsleid. Vereseerumist mõõdeti 25(OH)D, parathormooni, kaltsiumi ja ioniseeritud kaltsiumi, testosterooni ja kortisooli sisaldust 4 korda uuringuperioodi vältel ja mõlema käe pigistusjõu test tehti samuti 4 korda uuringuperioodi jooksul. Interventsioonirühmas statistiliselt olulist vereseerumi 25(OH)D langust uuringuperioodi jooksul ei leitud 47.2 nmol/l > 52.2 nmol/l. Soovituslikku D-vitamiini tase (>75 nmol/l) esines u. 15% uuritavatest 1200IU manustamisrühmas. Platseeborühmas esines kõigis ajapunktides statistiliselt oluline vereseerumi 25(OH)D langus 49.8 nmol/l>29.9 nmol/l. Soovituslikku D-vitamiini taset ei esinenud ühelgil uuritaval talvel ja kevadel. D-vitamiini kriitilise defitsiidi taseme (< 25 nmol/l) maksimum oli Märtsis 65%-l uuritavatest. Parathormooni, kaltsiumi ja ioniseeritud kaltsiumi, testosterooni ja kortisooli vereseerumi sisalduses olulisi erinevusi uuringurühmade vahel ei leitud. Käe pigistusjõu testides ei esinenud rühmade vahel ühelgil uuringuhetkel statistiliselt olulisi erinevusi.

III uuring. Kolmandas, 10 kuulises prospektiivses randomiseeritud kaksikpimedas uuringus osales kokku 112 meesajateenijat. Uuritavad jagati randomiseerimise käigus kahte uuringugruppi: 55 uuritavat 600IU D-vitamiin manustamise rühma ja 57 uuritavat 4000IU manustamise rühma. Füüsilise võimekuse (APFT) ja käe pigistusjõu teste sooritati uuringu vältel kokku kolmel korral. Vereseerumi 25(OH)D, parathormooni, kaltsiumi ja ioniseeritud kaltsiumi sisaldust määrati kokku nelja korral uuringu ajal. Kehakaal määrati samuti neljal korral uuringu jooksul vereanalüüsidega samal ajal. 600IU manustamise rühmas oli statistiliselt oluliselt madalamad vereseerumi 25(OH)D näitajad koos selge langustrendiga 77.3 nmol/l > 46.1 nmol/l võrreldes 4000IU manustamisrühmaga 77.3 nmol/l >69.8 nmol/l. Mitte ükski uuritavates ei saavutanud soovituslikku vereseerumi 25(OH)D normiväärtust (>75 nmol/l) jaanuaris ja mais 600IU manustamise rühmas. Kriitilist D-vitamiini defitsiiti (<25 nmo/l) esines mõlemas rühmas keskmisel 6% juhtudest talvel ja kevadel. Parathormooni, kaltsiumi ja ioniseeritud kaltsiumi vereseerumi sisalduses olulisi erinevusi uuringurühmade vahel ei leitud, kuid esinesid normipiirides keskmiste väärtuste kõikumised uuringurühmade siseselt. Kehakaalu seoseid D-vitamiini manustamisel 25(OH)D vereseerumi tasemetele ei leitud. Füüsiliste testide ja käepigistusjõu testidel ei esinenud uuritavate rühmade vahel statistilisi olulisi erinevusi.

Kokkuvõttes esineb tervetel Eesti noortel meestel ajateenistuse ajal oluline D-vitamiini defitsiidi ning kõrge kriitilise defitsiidi risk talvel ja kevadel ilma kaasneva D-vitamiini manustamiseta. D-vitamiini pikaajaline manustamine annuses 600IU ei anna positiivset efekti vereseerumi 25(OH)D tasemele ning 1200IU manustamine annab minimaalse efekti võrrelduna 4000IU manustamisega ajateenijatel ajateenistuse ajal. Kaasnevalt ei leitud uuringute käigus olulisi mõjusid parathormooni, kaltsiumi, ioniseeritud kaltsiumi, testosterooni ja kortisooli vereseerumi tasemetele ning kehakaalu seoseid D-vitamiini tasemele. Samuti leiti, et D-vitamiini lisamanustamine ei anna positiivset efekti füüsilisele võimekusele ning defitsiit ega ka kriitiline defitsiit ei oma negatiivset toimet füüsilisele võimekusele ajateenistuse käigus.

ACKNOWLEDGEMENTS

This work is dedicated to all the people who love sun…

PUBLICATIONS

CURRICULUM VITAE

Name: Leho Rips
Date of birth: October 30, 1973 Tartu, Estonia
Contact: Tartu University Hospital,
                Puusepa 1A, Tartu 50406, Estonia
Mob: +372 513 3474
E-mail: leho.rips@gmail.com

Education:
1988–1992   Paide Gymnasium
1993–1999   Tartu University, Medical Faculty

Postgraduate education:
1999–2000   Tartu University Clinics, Estonia, internship
2000–2005   Tartu University Clinics, Estonia, orthopaedic resident
2004   Helsinki University Hospital, Finland, orthopaedic resident

Professional experience:
2005–2020   Tammisaari Hospital, Finland. Consultant orthopaedic surgeon
2006–2011   Tartu University Hospital, Orthopaedic and Traumatology Clinic, orthopaedic surgeon
2008–   Medex, orthopaedic surgeon
2010–   Estonian Defence Forces, consultant orthopaedic surgeon
2013–   Tartu University Hospital, Sports Medicine and Rehabilitation Clinic, Sports Trautmatology Center, orthopaedic surgeon
2020–2021   Lappeenranta Hospital, Finland. Consultant orthopaedic surgeon
2021–2024   Lohja Hospital, Finland. Consultant orthopaedic surgeon
2022–   University of Tartu, Department of Sports Medicine and Rehabilitation, assistant

Professional societies:
1999–2000   Estonian Young Doctor`s Association
2001–   Estonian Orthopaedic Society
2008–   Estonian Arthroscopy and Sports Traumatology Society
2007–   European Society of Sports Traumatology Knee Surgery and Arthroscopy

Scientific work:
10 scientific articles published in international journals, 11 scientific articles published in Estonian journals, 24 posters and oral presentations at Estonian and international conferences.

Publications 1.1:

1. Chahla, J., Kunze, K.N., LaPrade, R.F., Getgood, A., Cohen, M., Gelber, P., Barenius, B., Pujol, N., Leyes, M., Akoto, R., Fritsch, B., Margheritini, F., Rips, L., Kautzner, J., Duthon, V., Togninalli, D., Giacamo, Z., Graveleau, N., Zaffagnini, S., Engbretsen, L., & Robinson, J. (2020). The posteromedial corner of the knee: an international expert consensus statement on diagnosis, classification, treatment, and rehabilitation. *Knee Surgery Sports Traumatology Arthroscopy. 29(9), 2976–2986.* DOI: 10.1007/s00167-020-06336-3.
2. Dobbe, J.G.G., Streekstra, G.J., Blankevoort, L., Wiegerinck, J.I., Maas, M., Zwiers, R., Van Dijk, C.N., Plaaß, C., Rips, L., Mansur, N.S.B., Sampath-kumar, K., Ovidiu, M.G., Russo, A., Burg, A., Kurup, H., Boszczyk, A., Gerards, R.M., Barwick, T., Jayaprasad, P.S., Kim, D., & Upadhyay, V. (2019). Exorotated radiographic views have additional diagnostic value in detecting an osseous impediment in patients with posterior ankle impingement. *Journal of Isakos, 4* (4), 181−187. DOI: 10.1136/jisakos-2019-000272.
3. Rips, L., Rahu, M., Kuik, R., Varblane, A., Olveti, I., Ööpik, V., Mölder, H., Timpmann, S., Tammaru, M., Toom, A., Kartus, J.-T., & Gapeyeva, H. (2020). Self-Reported Knee Pain Does Not Impact Physical Training Negatively in Conscripts. *Military Medicine, 7−8.* DOI: 10.1093/milmed/usz486.
4. Rips, L., Luik, M., Koovit, T., & Rahu, M. (2022). Lower leg muscle recovery takes at least 12 months for functional tests to recover after late reconstruction of the tibialis posterior tendon retinaculum. *BMJ Case Reports, 15* (1), e247273. DOI: 10.1136/bcr-2021-247273.
5. Rips, L., Toom, A., Kuik, R., Varblane, A., Mölder, H., Tammaru, M., Kull, M., Ööpik, V., Kartus, J.-T., Gapeyeva, H., & Rahu, M. (2022). Seven-month wintertime supplementation of 1200 IU vitamin D has no effect on hand grip strength in young, physically active males: A randomized, controlled study. *Journal of the International Society of Sports Nutrition, 19* (1), 437−454. DOI: 10.1080/15502783.2022.2100718.
6. Rips, L., Toom, A., Kuik, R., Varblane, A., Mölder, H., Kull, M., Kartus, J.-T., Gapeyeva, H., & Rahu, M. (2023). Severe deficiency of vitamin D has no negative effect on physical performance during military training. *The Journal of Sports Medicine and Physical Fitness, 63* (2), 329−338. DOI: 10.23736/S0022-4707.22.14123-X.
7. Rips, L., Toom, A., Kuik, R., Varblane, A., Mölder, H., Kibur, R., Laidvere, M., Kull, M., Kartus, J.-T., Gapeyeva, H., & Rahu, M. (2024). High dose vitamin D supplementation decreases the risk of deficiency in male conscripts, but has no effect on physical performance – a randomized study. *Journal of Experimental Orthopaedics*, e12023. https://doi.org/10.1002/jeo2.12023.
8. Toom, A., Fischer, K., Martson, A., Rips, L., & Haviko, T. (2005). Inter-observer reliability in the assessment of heterotopic ossification: proposal of a combined classification. *International Orthopaedics, 29*(3), 156-159.

9. Toom, A., Haviko, T., & Rips, L. (2001). Heterotopic ossification after total hip arthroplasty. *International Orthopaedics, 24*(6) 323-326.

10. Vähi, I., Rips, L., Varblane, A., & Pääsuke, M. (2023). Musculoskeletal injury risk in a military cadet population participating in an injury-prevention program. *Medicina, 59* (2). DOI: 10.3390/medicina59020356.

11. Ööpik, V., Timpmann, S., Rips, L., Olveti, I., Kõiv, K., Mooses, M., Mölder, H. Varblane, A. Lille, H.-R., & Gapeyeva, H. (2017). Anabolic adaptations occur in conscripts during basic military training despite high prevalence of vitamin D deficiency and decrease in iron status. *Military Medicine, 182*(3):e1810-e1818. doi: 10.7205/MILMED-D-16-00113.

ELULOOKIRJELDUS

Nimi: Leho Rips
Sünniaeg: 30. oktoober 1973, Tartu, Eesti
Aadress: Tartu Ülikooli Kliinikum,
                Puusepa 1A, Tartu 50406, Eesti
Mobiil: +372 513 3474
E-mail: leho.rips@gmail.com

Haridus:
1988–1992   Paide Gümnaasium
1993–1999   Tartu Ülikool, Arstiteaduskond

Erialane haridustee:
1999–2000   Tartu Ülikool Kliinikum, intern
2000–2005   Tartu Ülikooli Kliinikum, ortopeedia resident
2004   Helsingi Ülikooli Haigla, ortopeedia resident

Teenistuskäik:
2005–2020   Tammisaari Haigla, Soome, ortopeed
2006–2011   Tartu Ülikooli Kliinikum, Ortopeedia ja traumatoloogia kliinik,
            ortopeed
2008–   Medex, Tartu, ortopeed
2010–   Eesti Kaitsevägi, ortopeed
2013–   Tartu Ülikooli Kliinikum, Spordimeditsiini ja taastusravi kliinik,
            Sporditraumatoloogia keskus, ortopeed
2020–2021   Lappenranta Haigla, Soome, ortopeed
2021–2024   Lohja Haigla, Soome, ortopeed
2022–   Tartu Ülikool, Spordimeditsiini ja taastusravi Kliinik, assistent

Ühiskondlik tegevus ja seltsid:
1999–2000   Eesti Nooremarstide assotsiatsioon
2001–   Eesti Ortopeedia Selts
2008–   Eesti Artroskoopia ja Sporditraumatoloogia Selts
2007–   European Society of Sports Traumatology Knee Surgery and
            Arthroscopy

Teadustöö:
10 teadusartikklit rahvusvahelistes teadusajakirjades. 11 teadusartiklit Eesti aja-
kirjades. 24 postrit ja suulist ettekannet rahvusvahelistel ja Eesti konverentsidel.

Publikatsioonid 1.1:
1. Chahla, J., Kunze, K.N., LaPrade, R.F., Getgood, A., Cohen, M., Gelber, P., Barenius, B., Pujol, N., Leyes, M., Akoto, R., Fritsch, B., Margheritini, F., Rips, L., Kautzner, J., Duthon, V., Togninalli, D., Giacamo, Z., Graveleau, N., Zaffagnini, S., Engbretsen, L., & Robinson, J. (2020). The posteromedial corner of the knee: an international expert consensus statement on diagnosis, classification, treatment, and rehabilitation. *Knee Surgery Sports Traumatology Arthroscopy. 29(9), 2976–2986.* DOI: 10.1007/s00167-020-06336-3.
2. Dobbe, J.G.G., Streekstra, G.J., Blankevoort, L., Wiegerinck, J.I., Maas, M., Zwiers, R., Van Dijk, C.N., Plaaß, C., Rips, L., Mansur, N.S.B., Sampathkumar, K., Ovidiu, M.G., Russo, A., Burg, A., Kurup, H., Boszczyk, A., Gerards, R.M., Barwick, T., Jayaprasad, P.S., Kim, D., & Upadhyay, V. (2019). Exorotated radiographic views have additional diagnostic value in detecting an osseous impediment in patients with posterior ankle impingement. *Journal of Isakos, 4* (4), 181−187. DOI: 10.1136/jisakos-2019-000272.
3. Rips, L., Rahu, M., Kuik, R., Varblane, A., Olveti, I., Ööpik, V., Mölder, H., Timpmann, S., Tammaru, M., Toom, A., Kartus, J.-T., & Gapeyeva, H. (2020). Self-Reported Knee Pain Does Not Impact Physical Training Negatively in Conscripts. *Military Medicine, 7−8.* DOI: 10.1093/milmed/usz486.
4. Rips, L., Luik, M., Koovit, T., & Rahu, M. (2022). Lower leg muscle recovery takes at least 12 months for functional tests to recover after late reconstruction of the tibialis posterior tendon retinaculum. *BMJ Case Reports, 15* (1), e247273. DOI: 10.1136/bcr-2021-247273.
5. Rips, L., Toom, A., Kuik, R., Varblane, A., Mölder, H., Tammaru, M., Kull, M., Ööpik, V., Kartus, J.-T., Gapeyeva, H., & Rahu, M. (2022). Seven-month wintertime supplementation of 1200 IU vitamin D has no effect on hand grip strength in young, physically active males: A randomized, controlled study. *Journal of the International Society of Sports Nutrition, 19* (1), 437−454. DOI: 10.1080/15502783.2022.2100718.
6. Rips, L., Toom, A., Kuik, R., Varblane, A., Mölder, H., Kull, M., Kartus, J.-T., Gapeyeva, H., & Rahu, M. (2023). Severe deficiency of vitamin D has no negative effect on physical performance during military training. *The Journal of Sports Medicine and Physical Fitness, 63* (2), 329−338. DOI: 10.23736/S0022-4707.22.14123-X.
7. Rips, L., Toom, A., Kuik, R., Varblane, A., Mölder, H., Kibur, R., Laidvere, M., Kull, M., Kartus, J.-T., Gapeyeva, H., & Rahu, M. (2024). High dose vitamin D supplementation decreases the risk of deficiency in male conscripts, but has no effect on physical performance – a randomized study. *Journal of Experimental Orthopaedics*, e12023. https://doi.org/10.1002/jeo2.12023.
8. Toom, A., Fischer, K., Martson, A., Rips, L., & Haviko, T. (2005). Interobserver reliability in the assessment of heterotopic ossification: proposal of a combined classification. *International Orthopaedics, 29*(3), 156–159.
9. Toom, A., Haviko, T., & Rips, L. (2001). Heterotopic ossification after total hip arthroplasty. *International Orthopaedics, 24*(6) 323–326.

10. Vähi, I., Rips, L., Varblane, A., & Pääsuke, M. (2023). Musculoskeletal injury risk in a military cadet population participating in an injury-prevention program. *Medicina, 59* (2). DOI: 10.3390/medicina59020356.

11. Ööpik, V., Timpmann, S., Rips, L., Olveti, I., Kõiv, K., Mooses, M., Mölder, H. Varblane, A. Lille, H.-R., & Gapeyeva, H. (2017). Anabolic adaptations occur in conscripts during basic military training despite high prevalence of vitamin D deficiency and decrease in iron status. *Military Medicine, 182*(3):e1810-e1818. doi: 10.7205/MILMED-D-16-00113.

DISSERTATIONES MEDICINAE
UNIVERSITATIS TARTUENSIS

1. **Heidi-Ingrid Maaroos**. The natural course of gastric ulcer in connection with chronic gastritis and *Helicobacter pylori*. Tartu, 1991.
2. **Mihkel Zilmer**. Na-pump in normal and tumorous brain tissues: Structural, functional and tumorigenesis aspects. Tartu, 1991.
3. **Eero Vasar**. Role of cholecystokinin receptors in the regulation of behaviour and in the action of haloperidol and diazepam. Tartu, 1992.
4. **Tiina Talvik**. Hypoxic-ischaemic brain damage in neonates (clinical, biochemical and brain computed tomographical investigation). Tartu, 1992.
5. **Ants Peetsalu**. Vagotomy in duodenal ulcer disease: A study of gastric acidity, serum pepsinogen I, gastric mucosal histology and *Helicobacter pylori*. Tartu, 1992.
6. **Marika Mikelsaar**. Evaluation of the gastrointestinal microbial ecosystem in health and disease. Tartu, 1992.
7. **Hele Everaus**. Immuno-hormonal interactions in chronic lymphocytic leukaemia and multiple myeloma. Tartu, 1993.
8. **Ruth Mikelsaar**. Etiological factors of diseases in genetically consulted children and newborn screening: dissertation for the commencement of the degree of doctor of medical sciences. Tartu, 1993.
9. **Agu Tamm**. On metabolic action of intestinal microflora: clinical aspects. Tartu, 1993.
10. **Katrin Gross**. Multiple sclerosis in South-Estonia (epidemiological and computed tomographical investigations). Tartu, 1993.
11. **Oivi Uibo**. Childhood coeliac disease in Estonia: occurrence, screening, diagnosis and clinical characterization. Tartu, 1994.
12. **Viiu Tuulik**. The functional disorders of central nervous system of chemistry workers. Tartu, 1994.
13. **Margus Viigimaa**. Primary haemostasis, antiaggregative and anticoagulant treatment of acute myocardial infarction. Tartu, 1994.
14. **Rein Kolk**. Atrial versus ventricular pacing in patients with sick sinus syndrome. Tartu, 1994.
15. **Toomas Podar**. Incidence of childhood onset type 1 diabetes mellitus in Estonia. Tartu, 1994.
16. **Kiira Subi**. The laboratory surveillance of the acute respiratory viral infections in Estonia. Tartu, 1995.
17. **Irja Lutsar**. Infections of the central nervous system in children (epidemiologic, diagnostic and therapeutic aspects, long term outcome). Tartu, 1995.
18. **Aavo Lang**. The role of dopamine, 5-hydroxytryptamine, sigma and NMDA receptors in the action of antipsychotic drugs. Tartu, 1995.
19. **Andrus Arak**. Factors influencing the survival of patients after radical surgery for gastric cancer. Tartu, 1996.

20. **Tõnis Karki**. Quantitative composition of the human lactoflora and method for its examination. Tartu, 1996.
21. **Reet Mändar**. Vaginal microflora during pregnancy and its transmission to newborn. Tartu, 1996.
22. **Triin Remmel**. Primary biliary cirrhosis in Estonia: epidemiology, clinical characterization and prognostication of the course of the disease. Tartu, 1996.
23. **Toomas Kivastik**. Mechanisms of drug addiction: focus on positive reinforcing properties of morphine. Tartu, 1996.
24. **Paavo Pokk**. Stress due to sleep deprivation: focus on $GABA_A$ receptor-chloride ionophore complex. Tartu, 1996.
25. **Kristina Allikmets**. Renin system activity in essential hypertension. Associations with atherothrombogenic cardiovascular risk factors and with the efficacy of calcium antagonist treatment. Tartu, 1996.
26. **Triin Parik**. Oxidative stress in essential hypertension: Associations with metabolic disturbances and the effects of calcium antagonist treatment. Tartu, 1996.
27. **Svetlana Päi**. Factors promoting heterogeneity of the course of rheumatoid arthritis. Tartu, 1997.
28. **Maarike Sallo**. Studies on habitual physical activity and aerobic fitness in 4 to 10 years old children. Tartu, 1997.
29. **Paul Naaber**. *Clostridium difficile* infection and intestinal microbial ecology. Tartu, 1997.
30. **Rein Pähkla**. Studies in pinoline pharmacology. Tartu, 1997.
31. **Andrus Juhan Voitk**. Outpatient laparoscopic cholecystectomy. Tartu, 1997.
32. **Joel Starkopf**. Oxidative stress and ischaemia-reperfusion of the heart. Tartu, 1997.
33. **Janika Kõrv**. Incidence, case-fatality and outcome of stroke. Tartu, 1998.
34. **Ülla Linnamägi**. Changes in local cerebral blood flow and lipid peroxidation following lead exposure in experiment. Tartu, 1998.
35. **Ave Minajeva**. Sarcoplasmic reticulum function: comparison of atrial and ventricular myocardium. Tartu, 1998.
36. **Oleg Milenin**. Reconstruction of cervical part of esophagus by revascularised ileal autografts in dogs. A new complex multistage method. Tartu, 1998.
37. **Sergei Pakriev**. Prevalence of depression, harmful use of alcohol and alcohol dependence among rural population in Udmurtia. Tartu, 1998.
38. **Allen Kaasik**. Thyroid hormone control over β-adrenergic signalling system in rat atria. Tartu, 1998.
39. **Vallo Matto**. Pharmacological studies on anxiogenic and antiaggressive properties of antidepressants. Tartu, 1998.
40. **Maire Vasar**. Allergic diseases and bronchial hyperreactivity in Estonian children in relation to environmental influences. Tartu, 1998.
41. **Kaja Julge**. Humoral immune responses to allergens in early childhood. Tartu, 1998.

42. **Heli Grünberg**. The cardiovascular risk of Estonian schoolchildren. A cross-sectional study of 9-, 12- and 15-year-old children. Tartu, 1998.
43. **Epp Sepp**. Formation of intestinal microbial ecosystem in children. Tartu, 1998.
44. **Mai Ots**. Characteristics of the progression of human and experimental glomerulopathies. Tartu, 1998.
45. **Tiina Ristimäe**. Heart rate variability in patients with coronary artery disease. Tartu, 1998.
46. **Leho Kõiv**. Reaction of the sympatho-adrenal and hypothalamo-pituitary-adrenocortical system in the acute stage of head injury. Tartu, 1998.
47. **Bela Adojaan**. Immune and genetic factors of childhood onset IDDM in Estonia. An epidemiological study. Tartu, 1999.
48. **Jakov Shlik**. Psychophysiological effects of cholecystokinin in humans. Tartu, 1999.
49. **Kai Kisand**. Autoantibodies against dehydrogenases of α-ketoacids. Tartu, 1999.
50. **Toomas Marandi**. Drug treatment of depression in Estonia. Tartu, 1999.
51. **Ants Kask**. Behavioural studies on neuropeptide Y. Tartu, 1999.
52. **Ello-Rahel Karelson**. Modulation of adenylate cyclase activity in the rat hippocampus by neuropeptide galanin and its chimeric analogs. Tartu, 1999.
53. **Tanel Laisaar**. Treatment of pleural empyema — special reference to intrapleural therapy with streptokinase and surgical treatment modalities. Tartu, 1999.
54. **Eve Pihl**. Cardiovascular risk factors in middle-aged former athletes. Tartu, 1999.
55. **Katrin Õunap**. Phenylketonuria in Estonia: incidence, newborn screening, diagnosis, clinical characterization and genotype/phenotype correlation. Tartu, 1999.
56. **Siiri Kõljalg**. *Acinetobacter* – an important nosocomial pathogen. Tartu, 1999.
57. **Helle Karro**. Reproductive health and pregnancy outcome in Estonia: association with different factors. Tartu, 1999.
58. **Heili Varendi**. Behavioral effects observed in human newborns during exposure to naturally occurring odors. Tartu, 1999.
59. **Anneli Beilmann**. Epidemiology of epilepsy in children and adolescents in Estonia. Prevalence, incidence, and clinical characteristics. Tartu, 1999.
60. **Vallo Volke**. Pharmacological and biochemical studies on nitric oxide in the regulation of behaviour. Tartu, 1999.
61. **Pilvi Ilves**. Hypoxic-ischaemic encephalopathy in asphyxiated term infants. A prospective clinical, biochemical, ultrasonographical study. Tartu, 1999.
62. **Anti Kalda**. Oxygen-glucose deprivation-induced neuronal death and its pharmacological prevention in cerebellar granule cells. Tartu, 1999.
63. **Eve-Irene Lepist**. Oral peptide prodrugs – studies on stability and absorption. Tartu, 2000.

64. **Jana Kivastik**. Lung function in Estonian schoolchildren: relationship with anthropometric indices and respiratory symptomas, reference values for dynamic spirometry. Tartu, 2000.

65. **Karin Kull**. Inflammatory bowel disease: an immunogenetic study. Tartu, 2000.

66. **Kaire Innos**. Epidemiological resources in Estonia: data sources, their quality and feasibility of cohort studies. Tartu, 2000.

67. **Tamara Vorobjova**. Immune response to *Helicobacter pylori* and its association with dynamics of chronic gastritis and epithelial cell turnover in antrum and corpus. Tartu, 2001.

68. **Ruth Kalda**. Structure and outcome of family practice quality in the changing health care system of Estonia. Tartu, 2001.

69. **Annika Krüüner**. *Mycobacterium tuberculosis* – spread and drug resistance in Estonia. Tartu, 2001.

70. **Marlit Veldi**. Obstructive Sleep Apnoea: Computerized Endopharyngeal Myotonometry of the Soft Palate and Lingual Musculature. Tartu, 2001.

71. **Anneli Uusküla**. Epidemiology of sexually transmitted diseases in Estonia in 1990–2000. Tartu, 2001.

72. **Ade Kallas**. Characterization of antibodies to coagulation factor VIII. Tartu, 2002.

73. **Heidi Annuk**. Selection of medicinal plants and intestinal lactobacilli as antimicrobil components for functional foods. Tartu, 2002.

74. **Aet Lukmann**. Early rehabilitation of patients with ischaemic heart disease after surgical revascularization of the myocardium: assessment of health-related quality of life, cardiopulmonary reserve and oxidative stress. A clinical study. Tartu, 2002.

75. **Maigi Eisen**. Pathogenesis of Contact Dermatitis: participation of Oxidative Stress. A clinical – biochemical study. Tartu, 2002.

76. **Piret Hussar**. Histology of the post-traumatic bone repair in rats. Elaboration and use of a new standardized experimental model – bicortical perforation of tibia compared to internal fracture and resection osteotomy. Tartu, 2002.

77. **Tõnu Rätsep**. Aneurysmal subarachnoid haemorrhage: Noninvasive monitoring of cerebral haemodynamics. Tartu, 2002.

78. **Marju Herodes**. Quality of life of people with epilepsy in Estonia. Tartu, 2003.

79. **Katre Maasalu**. Changes in bone quality due to age and genetic disorders and their clinical expressions in Estonia. Tartu, 2003.

80. **Toomas Sillakivi**. Perforated peptic ulcer in Estonia: epidemiology, risk factors and relations with *Helicobacter pylori*. Tartu, 2003.

81. **Leena Puksa**. Late responses in motor nerve conduction studies. F and A waves in normal subjects and patients with neuropathies. Tartu, 2003.

82. **Krista Lõivukene**. *Helicobacter pylori* in gastric microbial ecology and its antimicrobial susceptibility pattern. Tartu, 2003.

83. **Helgi Kolk**. Dyspepsia and *Helicobacter pylori* infection: the diagnostic value of symptoms, treatment and follow-up of patients referred for upper gastrointestinal endoscopy by family physicians. Tartu, 2003.

84. **Helena Soomer**. Validation of identification and age estimation methods in forensic odontology. Tartu, 2003.

85. **Kersti Oselin**. Studies on the human MDR1, MRP1, and MRP2 ABC transporters: functional relevance of the genetic polymorphisms in the *MDR1* and *MRP1* gene. Tartu, 2003.

86. **Jaan Soplepmann**. Peptic ulcer haemorrhage in Estonia: epidemiology, prognostic factors, treatment and outcome. Tartu, 2003.

87. **Margot Peetsalu**. Long-term follow-up after vagotomy in duodenal ulcer disease: recurrent ulcer, changes in the function, morphology and *Helicobacter pylori* colonisation of the gastric mucosa. Tartu, 2003.

88. **Kersti Klaamas**. Humoral immune response to *Helicobacter pylori* a study of host-dependent and microbial factors. Tartu, 2003.

89. **Pille Taba**. Epidemiology of Parkinson's disease in Tartu, Estonia. Prevalence, incidence, clinical characteristics, and pharmacoepidemiology. Tartu, 2003.

90. **Alar Veraksitš**. Characterization of behavioural and biochemical phenotype of cholecystokinin-2 receptor deficient mice: changes in the function of the dopamine and endopioidergic system. Tartu, 2003.

91. **Ingrid Kalev**. CC-chemokine receptor 5 (CCR5) gene polymorphism in Estonians and in patients with Type I and Type II diabetes mellitus. Tartu, 2003.

92. **Lumme Kadaja**. Molecular approach to the regulation of mitochondrial function in oxidative muscle cells. Tartu, 2003.

93. **Aive Liigant**. Epidemiology of primary central nervous system tumours in Estonia from 1986 to 1996. Clinical characteristics, incidence, survival and prognostic factors. Tartu, 2004.

94. **Andres, Kulla**. Molecular characteristics of mesenchymal stroma in human astrocytic gliomas. Tartu, 2004.

95. **Mari Järvelaid**. Health damaging risk behaviours in adolescence. Tartu, 2004.

96. **Ülle Pechter**. Progression prevention strategies in chronic renal failure and hypertension. An experimental and clinical study. Tartu, 2004.

97. **Gunnar Tasa**. Polymorphic glutathione S-transferases – biology and role in modifying genetic susceptibility to senile cataract and primary open angle glaucoma. Tartu, 2004.

98. **Tuuli Käämbre**. Intracellular energetic unit: structural and functional aspects. Tartu, 2004.

99. **Vitali Vassiljev**. Influence of nitric oxide syntase inhibitors on the effects of ethanol after acute and chronic ethanol administration and withdrawal. Tartu, 2004.

100. **Aune Rehema**. Assessment of nonhaem ferrous iron and glutathione redox ratio as markers of pathogeneticity of oxidative stress in different clinical groups. Tartu, 2004.

101. **Evelin Seppet**. Interaction of mitochondria and ATPases in oxidative muscle cells in normal and pathological conditions. Tartu, 2004.

102. **Eduard Maron**. Serotonin function in panic disorder: from clinical experiments to brain imaging and genetics. Tartu, 2004.

103. **Marje Oona**. *Helicobacter pylori* infection in children: epidemiological and therapeutic aspects. Tartu, 2004.

104. **Kersti Kokk**. Regulation of active and passive molecular transport in the testis. Tartu, 2005.

105. **Vladimir Järv**. Cross-sectional imaging for pretreatment evaluation and follow-up of pelvic malignant tumours. Tartu, 2005.

106. **Andre Õun**. Epidemiology of adult epilepsy in Tartu, Estonia. Incidence, prevalence and medical treatment. Tartu, 2005.

107. **Piibe Muda**. Homocysteine and hypertension: associations between homocysteine and essential hypertension in treated and untreated hypertensive patients with and without coronary artery disease. Tartu, 2005.

108. **Külli Kingo**. The interleukin-10 family cytokines gene polymorphisms in plaque psoriasis. Tartu, 2005.

109. **Mati Merila**. Anatomy and clinical relevance of the glenohumeral joint capsule and ligaments. Tartu, 2005.

110. **Epp Songisepp**. Evaluation of technological and functional properties of the new probiotic *Lactobacillus fermentum* ME-3. Tartu, 2005.

111. **Tiia Ainla**. Acute myocardial infarction in Estonia: clinical characteristics, management and outcome. Tartu, 2005.

112. **Andres Sell**. Determining the minimum local anaesthetic requirements for hip replacement surgery under spinal anaesthesia – a study employing a spinal catheter. Tartu, 2005.

113. **Tiia Tamme**. Epidemiology of odontogenic tumours in Estonia. Pathogenesis and clinical behaviour of ameloblastoma. Tartu, 2005.

114. **Triine Annus**. Allergy in Estonian schoolchildren: time trends and characteristics. Tartu, 2005.

115. **Tiia Voor**. Microorganisms in infancy and development of allergy: comparison of Estonian and Swedish children. Tartu, 2005.

116. **Priit Kasenõmm**. Indicators for tonsillectomy in adults with recurrent tonsillitis – clinical, microbiological and pathomorphological investigations. Tartu, 2005.

117. **Eva Zusinaite**. Hepatitis C virus: genotype identification and interactions between viral proteases. Tartu, 2005.

118. **Piret Kõll**. Oral lactoflora in chronic periodontitis and periodontal health. Tartu, 2006.

119. **Tiina Stelmach**. Epidemiology of cerebral palsy and unfavourable neurodevelopmental outcome in child population of Tartu city and county, Estonia Prevalence, clinical features and risk factors. Tartu, 2006.

120. **Katrin Pudersell**. Tropane alkaloid production and riboflavine excretion in the field and tissue cultures of henbane (*Hyoscyamus niger* L.). Tartu, 2006.
121. **Külli Jaako**. Studies on the role of neurogenesis in brain plasticity. Tartu, 2006.
122. **Aare Märtson**. Lower limb lengthening: experimental studies of bone regeneration and long-term clinical results. Tartu, 2006.
123. **Heli Tähepõld**. Patient consultation in family medicine. Tartu, 2006.
124. **Stanislav Liskmann**. Peri-implant disease: pathogenesis, diagnosis and treatment in view of both inflammation and oxidative stress profiling. Tartu, 2006.
125. **Ruth Rudissaar**. Neuropharmacology of atypical antipsychotics and an animal model of psychosis. Tartu, 2006.
126. **Helena Andreson**. Diversity of *Helicobacter pylori* genotypes in Estonian patients with chronic inflammatory gastric diseases. Tartu, 2006.
127. **Katrin Pruus**. Mechanism of action of antidepressants: aspects of serotoninergic system and its interaction with glutamate. Tartu, 2006.
128. **Priit Põder**. Clinical and experimental investigation: relationship of ischaemia/reperfusion injury with oxidative stress in abdominal aortic aneurysm repair and in extracranial brain artery endarterectomy and possibilities of protection against ischaemia using a glutathione analogue in a rat model of global brain ischaemia. Tartu, 2006.
129. **Marika Tammaru**. Patient-reported outcome measurement in rheumatoid arthritis. Tartu, 2006.
130. **Tiia Reimand**. Down syndrome in Estonia. Tartu, 2006.
131. **Diva Eensoo**. Risk-taking in traffic and Markers of Risk-Taking Behaviour in Schoolchildren and Car Drivers. Tartu, 2007.
132. **Riina Vibo**. The third stroke registry in Tartu, Estonia from 2001 to 2003: incidence, case-fatality, risk factors and long-term outcome. Tartu, 2007.
133. **Chris Pruunsild**. Juvenile idiopathic arthritis in children in Estonia. Tartu, 2007.
134. **Eve Õiglane-Šlik**. Angelman and Prader-Willi syndromes in Estonia. Tartu, 2007.
135. **Kadri Haller**. Antibodies to follicle stimulating hormone. Significance in female infertility. Tartu, 2007.
136. **Pille Ööpik**. Management of depression in family medicine. Tartu, 2007.
137. **Jaak Kals**. Endothelial function and arterial stiffness in patients with atherosclerosis and in healthy subjects. Tartu, 2007.
138. **Priit Kampus**. Impact of inflammation, oxidative stress and age on arterial stiffness and carotid artery intima-media thickness. Tartu, 2007.
139. **Margus Punab**. Male fertility and its risk factors in Estonia. Tartu, 2007.
140. **Alar Toom**. Heterotopic ossification after total hip arthroplasty: clinical and pathogenetic investigation. Tartu, 2007.

141. **Lea Pehme**. Epidemiology of tuberculosis in Estonia 1991–2003 with special regard to extrapulmonary tuberculosis and delay in diagnosis of pulmonary tuberculosis. Tartu, 2007.
142. **Juri Karjagin**. The pharmacokinetics of metronidazole and meropenem in septic shock. Tartu, 2007.
143. **Inga Talvik**. Inflicted traumatic brain injury shaken baby syndrome in Estonia – epidemiology and outcome. Tartu, 2007.
144. **Tarvo Rajasalu**. Autoimmune diabetes: an immunological study of type 1 diabetes in humans and in a model of experimental diabetes (in RIP-B7.1 mice). Tartu, 2007.
145. **Inga Karu**. Ischaemia-reperfusion injury of the heart during coronary surgery: a clinical study investigating the effect of hyperoxia. Tartu, 2007.
146. **Peeter Padrik**. Renal cell carcinoma: Changes in natural history and treatment of metastatic disease. Tartu, 2007.
147. **Neve Vendt**. Iron deficiency and iron deficiency anaemia in infants aged 9 to 12 months in Estonia. Tartu, 2008.
148. **Lenne-Triin Heidmets**. The effects of neurotoxins on brain plasticity: focus on neural Cell Adhesion Molecule. Tartu, 2008.
149. **Paul Korrovits**. Asymptomatic inflammatory prostatitis: prevalence, etiological factors, diagnostic tools. Tartu, 2008.
150. **Annika Reintam**. Gastrointestinal failure in intensive care patients. Tartu, 2008.
151. **Kristiina Roots**. Cationic regulation of Na-pump in the normal, Alzheimer's and CCK_2 receptor-deficient brain. Tartu, 2008.
152. **Helen Puusepp**. The genetic causes of mental retardation in Estonia: fragile X syndrome and creatine transporter defect. Tartu, 2009.
153. **Kristiina Rull**. Human chorionic gonadotropin beta genes and recurrent miscarriage: expression and variation study. Tartu, 2009.
154. **Margus Eimre**. Organization of energy transfer and feedback regulation in oxidative muscle cells. Tartu, 2009.
155. **Maire Link**. Transcription factors FoxP3 and AIRE: autoantibody associations. Tartu, 2009.
156. **Kai Haldre**. Sexual health and behaviour of young women in Estonia. Tartu, 2009.
157. **Kaur Liivak**. Classical form of congenital adrenal hyperplasia due to 21-hydroxylase deficiency in Estonia: incidence, genotype and phenotype with special attention to short-term growth and 24-hour blood pressure. Tartu, 2009.
158. **Kersti Ehrlich**. Antioxidative glutathione analogues (UPF peptides) – molecular design, structure-activity relationships and testing the protective properties. Tartu, 2009.
159. **Anneli Rätsep**. Type 2 diabetes care in family medicine. Tartu, 2009.
160. **Silver Türk**. Etiopathogenetic aspects of chronic prostatitis: role of mycoplasmas, coryneform bacteria and oxidative stress. Tartu, 2009.

161. **Kaire Heilman**. Risk markers for cardiovascular disease and low bone mineral density in children with type 1 diabetes. Tartu, 2009.
162. **Kristi Rüütel**. HIV-epidemic in Estonia: injecting drug use and quality of life of people living with HIV. Tartu, 2009.
163. **Triin Eller**. Immune markers in major depression and in antidepressive treatment. Tartu, 2009.
164. **Siim Suutre**. The role of TGF-β isoforms and osteoprogenitor cells in the pathogenesis of heterotopic ossification. An experimental and clinical study of hip arthroplasty. Tartu, 2010.
165. **Kai Kliiman**. Highly drug-resistant tuberculosis in Estonia: Risk factors and predictors of poor treatment outcome. Tartu, 2010.
166. **Inga Villa**. Cardiovascular health-related nutrition, physical activity and fitness in Estonia. Tartu, 2010.
167. **Tõnis Org**. Molecular function of the first PHD finger domain of Auto-immune Regulator protein. Tartu, 2010.
168. **Tuuli Metsvaht**. Optimal antibacterial therapy of neonates at risk of early onset sepsis. Tartu, 2010.
169. **Jaanus Kahu**. Kidney transplantation: Studies on donor risk factors and mycophenolate mofetil. Tartu, 2010.
170. **Koit Reimand**. Autoimmunity in reproductive failure: A study on associated autoantibodies and autoantigens. Tartu, 2010.
171. **Mart Kull**. Impact of vitamin D and hypolactasia on bone mineral density: a population based study in Estonia. Tartu, 2010.
172. **Rael Laugesaar**. Stroke in children – epidemiology and risk factors. Tartu, 2010.
173. **Mark Braschinsky**. Epidemiology and quality of life issues of hereditary spastic paraplegia in Estonia and implemention of genetic analysis in everyday neurologic practice. Tartu, 2010.
174. **Kadri Suija**. Major depression in family medicine: associated factors, recurrence and possible intervention. Tartu, 2010.
175. **Jarno Habicht**. Health care utilisation in Estonia: socioeconomic determinants and financial burden of out-of-pocket payments. Tartu, 2010.
176. **Kristi Abram**. The prevalence and risk factors of rosacea. Subjective disease perception of rosacea patients. Tartu, 2010.
177. **Malle Kuum**. Mitochondrial and endoplasmic reticulum cation fluxes: Novel roles in cellular physiology. Tartu, 2010.
178. **Rita Teek**. The genetic causes of early onset hearing loss in Estonian children. Tartu, 2010.
179. **Daisy Volmer**. The development of community pharmacy services in Estonia – public and professional perceptions 1993–2006. Tartu, 2010.
180. **Jelena Lissitsina**. Cytogenetic causes in male infertility. Tartu, 2011.
181. **Delia Lepik**. Comparison of gunshot injuries caused from Tokarev, Makarov and Glock 19 pistols at different firing distances. Tartu, 2011.
182. **Ene-Renate Pähkla**. Factors related to the efficiency of treatment of advanced periodontitis. Tartu, 2011.

183. **Maarja Krass**. L-Arginine pathways and antidepressant action. Tartu, 2011.
184. **Taavi Lai**. Population health measures to support evidence-based health policy in Estonia. Tartu, 2011.
185. **Tiit Salum**. Similarity and difference of temperature-dependence of the brain sodium pump in normal, different neuropathological, and aberrant conditions and its possible reasons. Tartu, 2011.
186. **Tõnu Vooder**. Molecular differences and similarities between histological subtypes of non-small cell lung cancer. Tartu, 2011.
187. **Jelena Štšepetova**. The characterisation of intestinal lactic acid bacteria using bacteriological, biochemical and molecular approaches. Tartu, 2011.
188. **Radko Avi**. Natural polymorphisms and transmitted drug resistance in Estonian HIV-1 CRF06_cpx and its recombinant viruses. Tartu, 2011, 116 p.
189. **Edward Laane**. Multiparameter flow cytometry in haematological malignancies. Tartu, 2011, 152 p.
190. **Triin Jagomägi**. A study of the genetic etiology of nonsyndromic cleft lip and palate. Tartu, 2011, 158 p.
191. **Ivo Laidmäe**. Fibrin glue of fish (*Salmo salar*) origin: immunological study and development of new pharmaceutical preparation. Tartu, 2012, 150 p.
192. **Ülle Parm**. Early mucosal colonisation and its role in prediction of invasive infection in neonates at risk of early onset sepsis. Tartu, 2012, 168 p.
193. **Kaupo Teesalu**. Autoantibodies against desmin and transglutaminase 2 in celiac disease: diagnostic and functional significance. Tartu, 2012, 142 p.
194. **Maksim Zagura**. Biochemical, functional and structural profiling of arterial damage in atherosclerosis. Tartu, 2012, 162 p.
195. **Vivian Kont**. Autoimmune regulator: characterization of thymic gene regulation and promoter methylation. Tartu, 2012, 134 p.
196. **Pirje Hütt**. Functional properties, persistence, safety and efficacy of potential probiotic lactobacilli. Tartu, 2012, 246 p.
197. **Innar Tõru**. Serotonergic modulation of CCK-4- induced panic. Tartu, 2012, 132 p.
198. **Sigrid Vorobjov**. Drug use, related risk behaviour and harm reduction interventions utilization among injecting drug users in Estonia: implications for drug policy. Tartu, 2012, 120 p.
199. **Martin Serg**. Therapeutic aspects of central haemodynamics, arterial stiffness and oxidative stress in hypertension. Tartu, 2012, 156 p.
200. **Jaanika Kumm**. Molecular markers of articular tissues in early knee osteoarthritis: a population-based longitudinal study in middle-aged subjects. Tartu, 2012, 159 p.
201. **Kertu Rünkorg**. Functional changes of dopamine, endopioid and endocannabinoid systems in CCK2 receptor deficient mice. Tartu, 2012, 125 p.
202. **Mai Blöndal**. Changes in the baseline characteristics, management and outcomes of acute myocardial infarction in Estonia. Tartu, 2012, 127 p.

203. **Jana Lass**. Epidemiological and clinical aspects of medicines use in children in Estonia. Tartu, 2012, 170 p.

204. **Kai Truusalu**. Probiotic lactobacilli in experimental persistent *Salmonella* infection. Tartu, 2013, 139 p.

205. **Oksana Jagur**. Temporomandibular joint diagnostic imaging in relation to pain and bone characteristics. Long-term results of arthroscopic treatment. Tartu, 2013, 126 p.

206. **Katrin Sikk**. Manganese-ephedrone intoxication – pathogenesis of neurological damage and clinical symptomatology. Tartu, 2013, 125 p.

207. **Kai Blöndal**. Tuberculosis in Estonia with special emphasis on drug-resistant tuberculosis: Notification rate, disease recurrence and mortality. Tartu, 2013, 151 p.

208. **Marju Puurand**. Oxidative phosphorylation in different diseases of gastric mucosa. Tartu, 2013, 123 p.

209. **Aili Tagoma**. Immune activation in female infertility: Significance of autoantibodies and inflammatory mediators. Tartu, 2013, 135 p.

210. **Liis Sabre**. Epidemiology of traumatic spinal cord injury in Estonia. Brain activation in the acute phase of traumatic spinal cord injury. Tartu, 2013, 135 p.

211. **Merit Lamp**. Genetic susceptibility factors in endometriosis. Tartu, 2013, 125 p.

212. **Erik Salum**. Beneficial effects of vitamin D and angiotensin II receptor blocker on arterial damage. Tartu, 2013, 167 p.

213. **Maire Karelson**. Vitiligo: clinical aspects, quality of life and the role of melanocortin system in pathogenesis. Tartu, 2013, 153 p.

214. **Kuldar Kaljurand**. Prevalence of exfoliation syndrome in Estonia and its clinical significance. Tartu, 2013, 113 p.

215. **Raido Paasma**. Clinical study of methanol poisoning: handling large outbreaks, treatment with antidotes, and long-term outcomes. Tartu, 2013, 96 p.

216. **Anne Kleinberg**. Major depression in Estonia: prevalence, associated factors, and use of health services. Tartu, 2013, 129 p.

217. **Triin Eglit**. Obesity, impaired glucose regulation, metabolic syndrome and their associations with high-molecular-weight adiponectin levels. Tartu, 2014, 115 p.

218. **Kristo Ausmees**. Reproductive function in middle-aged males: Associations with prostate, lifestyle and couple infertility status. Tartu, 2014, 125 p.

219. **Kristi Huik**. The influence of host genetic factors on the susceptibility to HIV and HCV infections among intravenous drug users. Tartu, 2014, 144 p.

220. **Liina Tserel**. Epigenetic profiles of monocytes, monocyte-derived macrophages and dendritic cells. Tartu, 2014, 143 p.

221. **Irina Kerna**. The contribution of *ADAM12* and *CILP* genes to the development of knee osteoarthritis. Tartu, 2014, 152 p.

222. **Ingrid Liiv**. Autoimmune regulator protein interaction with DNA-dependent protein kinase and its role in apoptosis. Tartu, 2014, 143 p.
223. **Liivi Maddison**. Tissue perfusion and metabolism during intra-abdominal hypertension. Tartu, 2014, 103 p.
224. **Krista Ress**. Childhood coeliac disease in Estonia, prevalence in atopic dermatitis and immunological characterisation of coexistence. Tartu, 2014, 124 p.
225. **Kai Muru**. Prenatal screening strategies, long-term outcome of children with marked changes in maternal screening tests and the most common syndromic heart anomalies in Estonia. Tartu, 2014, 189 p.
226. **Kaja Rahu**. Morbidity and mortality among Baltic Chernobyl cleanup workers: a register-based cohort study. Tartu, 2014, 155 p.
227. **Klari Noormets**. The development of diabetes mellitus, fertility and energy metabolism disturbances in a Wfs1-deficient mouse model of Wolfram syndrome. Tartu, 2014, 132 p.
228. **Liis Toome**. Very low gestational age infants in Estonia. Tartu, 2014, 183 p.
229. **Ceith Nikkolo**. Impact of different mesh parameters on chronic pain and foreign body feeling after open inguinal hernia repair. Tartu, 2014, 132 p.
230. **Vadim Brjalin**. Chronic hepatitis C: predictors of treatment response in Estonian patients. Tartu, 2014, 122 p.
231. **Vahur Metsna**. Anterior knee pain in patients following total knee arthroplasty: the prevalence, correlation with patellar cartilage impairment and aspects of patellofemoral congruence. Tartu, 2014, 130 p.
232. **Marju Kase**. Glioblastoma multiforme: possibilities to improve treatment efficacy. Tartu, 2015, 137 p.
233. **Riina Runnel**. Oral health among elementary school children and the effects of polyol candies on the prevention of dental caries. Tartu, 2015, 112 p.
234. **Made Laanpere**. Factors influencing women's sexual health and reproductive choices in Estonia. Tartu, 2015, 176 p.
235. **Andres Lust**. Water mediated solid state transformations of a polymorphic drug – effect on pharmaceutical product performance. Tartu, 2015, 134 p.
236. **Anna Klugman**. Functionality related characterization of pretreated wood lignin, cellulose and polyvinylpyrrolidone for pharmaceutical applications. Tartu, 2015, 156 p.
237. **Triin Laisk-Podar**. Genetic variation as a modulator of susceptibility to female infertility and a source for potential biomarkers. Tartu, 2015, 155 p.
238. **Mailis Tõnisson**. Clinical picture and biochemical changes in blood in children with acute alcohol intoxication. Tartu, 2015, 100 p.
239. **Kadri Tamme**. High volume haemodiafiltration in treatment of severe sepsis – impact on pharmacokinetics of antibiotics and inflammatory response. Tartu, 2015, 133 p.

240. **Kai Part**. Sexual health of young people in Estonia in a social context: the role of school-based sexuality education and youth-friendly counseling services. Tartu, 2015, 203 p.
241. **Urve Paaver**. New perspectives for the amorphization and physical stabilization of poorly water-soluble drugs and understanding their dissolution behavior. Tartu, 2015, 139 p.
242. **Aleksandr Peet**. Intrauterine and postnatal growth in children with HLA-conferred susceptibility to type 1 diabetes. Tartu. 2015, 146 p.
243. **Piret Mitt**. Healthcare-associated infections in Estonia – epidemiology and surveillance of bloodstream and surgical site infections. Tartu, 2015, 145 p.
244. **Merli Saare**. Molecular Profiling of Endometriotic Lesions and Endometria of Endometriosis Patients. Tartu, 2016, 129 p.
245. **Kaja-Triin Laisaar**. People living with HIV in Estonia: Engagement in medical care and methods of increasing adherence to antiretroviral therapy and safe sexual behavior. Tartu, 2016, 132 p.
246. **Eero Merilind**. Primary health care performance: impact of payment and practice-based characteristics. Tartu, 2016, 120 p.
247. **Jaanika Kärner**. Cytokine-specific autoantibodies in AIRE deficiency. Tartu, 2016, 182 p.
248. **Kaido Paapstel**. Metabolomic profile of arterial stiffness and early biomarkers of renal damage in atherosclerosis. Tartu, 2016, 173 p.
249. **Liidia Kiisk**. Long-term nutritional study: anthropometrical and clinicolaboratory assessments in renal replacement therapy patients after intensive nutritional counselling. Tartu, 2016, 207 p.
250. **Georgi Nellis**. The use of excipients in medicines administered to neonates in Europe. Tartu, 2017, 159 p.
251. **Aleksei Rakitin**. Metabolic effects of acute and chronic treatment with valproic acid in people with epilepsy. Tartu, 2017, 125 p.
252. **Eveli Kallas**. The influence of immunological markers to susceptibility to HIV, HBV, and HCV infections among persons who inject drugs. Tartu, 2017, 138 p.
253. **Tiina Freimann**. Musculoskeletal pain among nurses: prevalence, risk factors, and intervention. Tartu, 2017, 125 p.
254. **Evelyn Aaviksoo**. Sickness absence in Estonia: determinants and influence of the sick-pay cut reform. Tartu, 2017, 121 p.
255. **Kalev Nõupuu**. Autosomal-recessive Stargardt disease: phenotypic heterogeneity and genotype-phenotype associations. Tartu, 2017, 131 p.
256. **Ho Duy Binh**. Osteogenesis imperfecta in Vietnam. Tartu, 2017, 125 p.
257. **Uku Haljasorg**. Transcriptional mechanisms in thymic central tolerance. Tartu, 2017, 147 p.
258. **Živile Riispere**. IgA Nephropathy study according to the Oxford Classification: IgA Nephropathy clinical-morphological correlations, disease progression and the effect of renoprotective therapy. Tartu, 2017, 129 p.

259. **Hiie Soeorg**. Coagulase-negative staphylococci in gut of preterm neonates and in breast milk of their mothers. Tartu, 2017, 216 p.

260. **Anne-Mari Anton Willmore**. Silver nanoparticles for cancer research. Tartu, 2017, 132 p.

261. **Ott Laius**. Utilization of osteoporosis medicines, medication adherence and the trend in osteoporosis related hip fractures in Estonia. Tartu, 2017, 134 p.

262. **Alar Aab**. Insights into molecular mechanisms of asthma and atopic dermatitis. Tartu, 2017, 164 p.

263. **Sander Pajusalu**. Genome-wide diagnostics of Mendelian disorders: from chromosomal microarrays to next-generation sequencing. Tartu, 2017, 146 p.

264. **Mikk Jürisson**. Health and economic impact of hip fracture in Estonia. Tartu, 2017, 164 p.

265. **Kaspar Tootsi**. Cardiovascular and metabolomic profiling of osteo-arthritis. Tartu, 2017, 150 p.

266. **Mario Saare**. The influence of AIRE on gene expression – studies of transcriptional regulatory mechanisms in cell culture systems. Tartu, 2017, 172 p.

267. **Piia Jõgi**. Epidemiological and clinical characteristics of pertussis in Estonia. Tartu, 2018, 168 p.

268. **Elle Põldoja**. Structure and blood supply of the superior part of the shoulder joint capsule. Tartu, 2018, 116 p.

269. **Minh Son Nguyen**. Oral health status and prevalence of temporo-mandibular disorders in 65–74-year-olds in Vietnam. Tartu, 2018, 182 p.

270. **Kristian Semjonov**. Development of pharmaceutical quench-cooled molten and melt-electrospun solid dispersions for poorly water-soluble indomethacin. Tartu, 2018, 125 p.

271. **Janne Tiigimäe-Saar**. Botulinum neurotoxin type A treatment for sialorrhea in central nervous system diseases. Tartu, 2018, 109 p.

272. **Veiko Vengerfeldt**. Apical periodontitis: prevalence and etiopathogenetic aspects. Tartu, 2018, 150 p.

273. **Rudolf Bichele**. TNF superfamily and AIRE at the crossroads of thymic differentiation and host protection against *Candida albicans* infection. Tartu, 2018, 153 p.

274. **Olga Tšuiko**. Unravelling Chromosomal Instability in Mammalian Pre-implantation Embryos Using Single-Cell Genomics. Tartu, 2018, 169 p.

275. **Kärt Kriisa**. Profile of acylcarnitines, inflammation and oxidative stress in first-episode psychosis before and after antipsychotic treatment. Tartu, 2018, 145 p.

276. **Xuan Dung Ho**. Characterization of the genomic profile of osteosarcoma. Tartu, 2018, 144 p.

277. **Karit Reinson**. New Diagnostic Methods for Early Detection of Inborn Errors of Metabolism in Estonia. Tartu, 2018, 201 p.

278. **Mari-Anne Vals**. Congenital N-glycosylation Disorders in Estonia. Tartu, 2019, 148 p.

279. **Liis Kadastik-Eerme**. Parkinson's disease in Estonia: epidemiology, quality of life, clinical characteristics and pharmacotherapy. Tartu, 2019, 202 p.

280. **Hedi Hunt**. Precision targeting of intraperitoneal tumors with peptide-guided nanocarriers. Tartu, 2019, 179 p.

281. **Rando Porosk**. The role of oxidative stress in Wolfram syndrome 1 and hypothermia. Tartu, 2019, 123 p.

282. **Ene-Ly Jõgeda**. The influence of coinfections and host genetic factor on the susceptibility to HIV infection among people who inject drugs. Tartu, 2019, 126 p.

283. **Kristel Ehala-Aleksejev**. The associations between body composition, obesity and obesity-related health and lifestyle conditions with male reproductive function. Tartu, 2019, 138 p.

284. **Aigar Ottas**. The metabolomic profiling of psoriasis, atopic dermatitis and atherosclerosis. Tartu, 2019, 136 p.

285. **Elmira Gurbanova**. Specific characteristics of tuberculosis in low default, but high multidrug–resistance prison setting. Tartu, 2019, 129 p.

286. **Van Thai Nguyeni**. The first study of the treatment outcomes of patients with cleft lip and palate in Central Vietnam. Tartu, 2019, 144 p.

287. **Maria Yakoreva**. Imprinting Disorders in Estonia. Tartu, 2019, 187 p.

288. **Kadri Rekker**. The putative role of microRNAs in endometriosis pathogenesis and potential in diagnostics. Tartu, 2019, 140 p.

289. **Ülle Võhma**. Association between personality traits, clinical characteristics and pharmacological treatment response in panic disorder. Tartu, 2019, 121 p.

290. **Aet Saar**. Acute myocardial infarction in Estonia 2001–2014: towards risk-based prevention and management. Tartu, 2019, 124 p.

291. **Toomas Toomsoo**. Transcranial brain sonography in the Estonian cohort of Parkinson's disease. Tartu, 2019, 114 p.

292. **Lidiia Zhytnik**. Inter- and intrafamilial diversity based on genotype and phenotype correlations of Osteogenesis Imperfecta. Tartu, 2019, 224 p.

293. **Pilleriin Soodla**. Newly HIV-infected people in Estonia: estimation of incidence and transmitted drug resistance. Tartu, 2019, 194 p.

294. **Kristiina Ojamaa**. Epidemiology of gynecological cancer in Estonia. Tartu, 2020, 133 p.

295. **Marianne Saard**. Modern Cognitive and Social Intervention Techniques in Paediatric Neurorehabilitation for Children with Acquired Brain Injury. Tartu, 2020, 168 p.

296. **Julia Maslovskaja**. The importance of DNA binding and DNA breaks for AIRE-mediated transcriptional activation. Tartu, 2020, 162 p.

297. **Natalia Lobanovskaya**. The role of PSA-NCAM in the survival of retinal ganglion cells. Tartu, 2020, 105 p.

298. **Madis Rahu**. Structure and blood supply of the postero-superior part of the shoulder joint capsule with implementation of surgical treatment after anterior traumatic dislocation. Tartu, 2020, 104 p.

299. **Helen Zirnask**. Luteinizing hormone (LH) receptor expression in the penis and its possible role in pathogenesis of erectile disturbances. Tartu, 2020, 87 p.

300. **Kadri Toome**. Homing peptides for targeting of brain diseases. Tartu, 2020, 152 p.

301. **Maarja Hallik**. Pharmacokinetics and pharmacodynamics of inotropic drugs in neonates. Tartu, 2020, 172 p.

302. **Raili Müller**. Cardiometabolic risk profile and body composition in early rheumatoid arthritis. Tartu, 2020, 133 p.

303. **Sergo Kasvandik**. The role of proteomic changes in endometrial cells – from the perspective of fertility and endometriosis. Tartu, 2020, 191 p.

304. **Epp Kaleviste**. Genetic variants revealing the role of STAT1/STAT3 signaling cytokines in immune protection and pathology. Tartu, 2020, 189 p.

305. **Sten Saar**. Epidemiology of severe injuries in Estonia. Tartu, 2020, 104 p.

306. **Kati Braschinsky**. Epidemiology of primary headaches in Estonia and applicability of web-based solutions in headache epidemiology research. Tartu, 2020, 129 p.

307. **Helen Vaher**. MicroRNAs in the regulation of keratinocyte responses in *psoriasis vulgaris* and atopic dermatitis. Tartu, 2020, 242 p.

308. **Liisi Raam**. Molecular Alterations in the Pathogenesis of Two Chronic Dermatoses – Vitiligo and Psoriasis. Tartu, 2020, 164 p.

309. **Artur Vetkas**. Long-term quality of life, emotional health, and associated factors in patients after aneurysmal subarachnoid haemorrhage. Tartu, 2020, 127 p.

310. **Teele Kasepalu**. Effects of remote ischaemic preconditioning on organ damage and acylcarnitines' metabolism in vascular surgery. Tartu, 2020, 130 p.

311. **Prakash Lingasamy**. Development of multitargeted tumor penetrating peptides. Tartu, 2020, 246 p.

312. **Lille Kurvits.** Parkinson's disease as a multisystem disorder: whole transcriptome study in Parkinson's disease patients' skin and blood. Tartu, 2021, 142 p.

313. **Mariliis Põld.** Smoking, attitudes towards smoking behaviour, and nicotine dependence among physicians in Estonia: cross-sectional surveys 1982–2014. Tartu, 2021, 172 p.

314. **Triin Kikas**. Single nucleotide variants affecting placental gene expression and pregnancy outcome. Tartu, 2021, 160 p.

315. **Hedda Lippus-Metsaots**. Interpersonal violence in Estonia: prevalence, impact on health and health behaviour. Tartu, 2021, 172 p.

316. **Georgi Dzaparidze.** Quantification and evaluation of the diagnostic significance of adenocarcinoma-associated microenvironmental changes in the prostate using modern digital pathology solutions. Tartu, 2021, 132 p.

317. **Tuuli Sedman.** New avenues for GLP1 receptor agonists in the treatment of diabetes. Tartu, 2021, 118 p.

318. **Martin Padar.** Enteral nutrition, gastrointestinal dysfunction and intestinal biomarkers in critically ill patients. Tartu, 2021, 189 p.

319. **Siim Schneider.** Risk factors, etiology and long-term outcome in young ischemic stroke patients in Estonia. Tartu, 2021, 131 p.

320. **Konstantin Ridnõi.** Implementation and effectiveness of new prenatal diagnostic strategies in Estonia. Tartu, 2021, 191 p.

321. **Risto Vaikjärv.** Etiopathogenetic and clinical aspects of peritonsillar abscess. Tartu, 2021, 115 p.

322. **Liis Preem.** Design and characterization of antibacterial electrospun drug delivery systems for wound infections. Tartu, 2022, 220 p.

323. **Keerthie Dissanayake.** Preimplantation embryo-derived extracellular vesicles: potential as an embryo quality marker and their role during the embryo-maternal communication. Tartu, 2022, 203 p.

324. **Laura Viidik.** 3D printing in pharmaceutics: a new avenue for fabricating therapeutic drug delivery systems. Tartu, 2022, 139 p.

325. **Kasun Godakumara.** Extracellular vesicle mediated embryo-maternal communication – A tool for evaluating functional competency of pre-implantation embryos. Tartu, 2022, 176 p.

326. **Hindrek Teder.** Developing computational methods and workflows for targeted and whole-genome sequencing based non-invasive prenatal testing. Tartu, 2022, 138 p.

327. **Jana Tuusov.** Deaths caused by alcohol, psychotropic and other substances in Estonia: evidence based on forensic autopsies. Tartu, 2022, 157 p.

328. **Heigo Reima.** Colorectal cancer care and outcomes – evaluation and possibilities for improvement in Estonia. Tartu, 2022, 146 p.

329. **Liisa Kuhi.** A contribution of biomarker collagen type II neoepitope C2C in urine to the diagnosis and prognosis of knee osteoarthritis. Tartu, 2022, 157 p.

330. **Reeli Tamme.** Associations between pubertal hormones and physical activity levels, and subsequent bone mineral characteristics: a longitudinal study of boys aged 12–18. Tartu, 2022, 118 p.

331. **Deniss Sõritsa.** The impact of endometriosis and physical activity on female reproduction. Tartu, 2022, 152 p.

332. **Mohammad Mehedi Hasan.** Characterization of follicular fluid-derived extracellular vesicles and their contribution to periconception environment. Tartu, 2022, 194 p.

333. **Priya Kulkarni.** Osteoarthritis pathogenesis: an immunological passage through synovium-synovial fluid axis. Tartu, 2022, 268 p.

334. **Nigul Ilves.** Brain plasticity and network reorganization in children with perinatal stroke: a functional magnetic resonance imaging study. Tartu, 2022, 169 p.

335. **Marko Murruste.** Short- and long-term outcomes of surgical management of chronic pancreatitis. Tartu, 2022, 180 p.

336. **Marilin Ivask.** Transcriptomic and metabolic changes in the WFS1-deficient mouse model. Tartu, 2022, 158 p.

337. **Jüri Lieberg.** Results of surgical treatment and role of biomarkers in pathogenesis and risk prediction in patients with abdominal aortic aneurysm and peripheral artery disease. Tartu, 2022, 160 p.

338. **Sanna Puusepp.** Comparison of molecular genetics and morphological findings of childhood-onset neuromuscular disorders. Tartu, 2022, 216 p.

339. **Khan Nguyen Viet.** Chemical composition and bioactivity of extracts and constituents isolated from the medicinal plants in Vietnam and their nanotechnology-based delivery systems. Tartu, 2023, 172 p.

340. **Getnet Balcha Midekessa.** Towards understanding the colloidal stability and detection of Extracellular Vesicles. Tartu, 2023, 172 p.

341. **Kristiina Sepp.** Competency-based and person-centred community pharmacy practice – development and implementation in Estonia. Tartu, 2023, 242 p.

342. **Linda Sõber.** Impact of thyroid disease and surgery on patient's quality of voice and swallowing. Tartu, 2023, 114 p.

343. **Anni Lepland.** Precision targeting of tumour-associated macrophages in triple negative breast cancer. Tartu, 2023, 160 p.

344. **Sirje Sammul.** Prevalence and risk factors of arterial hypertension and cardiovascular mortality: 13-year longitudinal study among 35- and 55-year-old adults in Estonia and Sweden. Tartu, 2023, 158 p.

345. **Maarjaliis Paavo**. Short-Wavelength and Near-Infrared Autofluorescence Imaging in Recessive Stargardt Disease, Choroideremia, *PROM1*-Macular Dystrophy and Ocular Albinism. Tartu, 2023, 202 p.

346. **Kaspar Ratnik.** development of predictive multimarker test for preeclampsia in early and late pregnancy. Tartu, 2023, 134 p.

347. **Kärt Simre.** Development of coeliac disease in two populations with different environmental backgrounds. Tartu, 2023, 161 p.

348. **Qurat Ul Ain Reshi.** Characterization of the maternal reproductive tract and spermatozoa communication during periconception period via extracellular vesicles. Tartu, 2023, 182 p.

349. **Stanislav Tjagur.** *Mycoplasma genitalium* and other sexually transmitted infections causing urethritis – their prevalence, impact on male fertility parameters and prostate health. Tartu, 2023, 225 p.

350. **Lagle Lehes.** The first study of voice and resonance related treatment outcomes of Estonian cleft palate children. Tartu, 2023, 126 p.

351. **Liis Ilves.** Metabolomic profiling of chronic inflammatory skin diseases. Tartu, 2023, 146 p.

352. **Marina Šunina**. Flow cytometric analysis of T and B cell properties in healthy donors and subjects with vitiligo. Tartu, 2023, 164 p.

353. **Jaanus Suumann.** Gastric biomarkers and their dynamics as a less invasive method to evaluate stomach health in bariatric surgery patients. Tartu, 2023, 122 p.

354. **Ele Hanson.** Clinical and biochemical markers for the prediction and early diagnosis of pregnancy related complications. Tartu, 2023, 145 p.

355. **Priit Pauklin.** Hemodynamic and biochemical characteristics of patients with atrial fibrillation and anticoagulation of ≥65-year-old patients with atrial fibrillation in Estonia. Tartu, 2023, 144 p.

356. **Triinu Keskpaik.** Quality Indicators and Non-Ischemic Myocardial Injury in Emergency Medicine. Tartu, 2023, 121 p.

357. **Laura Roht.** Hereditary colorectal cancer syndromes in Estonia. Tartu, 2023, 178 p.

358. **Norman Ilves.** Risk factors and onset time of periventricular hemorrhagic infarction in preterm born children and periventricular venous infarction in term born children. Tartu, 2024, 177 p.

359. **Edgar Lipping.** Postoperative antibacterial therapy in complicated appendicitis and appendectomy in pregnancy. Tartu, 2024, 121 p.

360. **Celia Teresa Pozo Ramos.** Preparation and assessment of antimicrobial electrospun matrices for prospective applications in wound healing. Tartu, 2024, 203 p.

361. **Karl Kuusik.** Effects of remote ischaemic preconditioning on arterial stiffness, organ damage and metabolomic profile in patients with lower extremity artery disease. Tartu, 2024, 173 p.

362. **Kelli Somelar-Duracz.** The molecular and cellular mechanisms of brain plasticity impairing factors. Tartu, 2024, 245 p.

363. **Aleksei Baburin.** Breast cancer incidence, mortality and survival in Estonia in the context of health care system changes and screening. Tartu, 2024, 130 p.

364. **Marina Loid.** Molecular and cellular determinants of healthy receptive and aged endometrium. Tartu, 2024, 159 p.

365. **Ulvi Vaher.** Epilepsy after ischemic perinatal stroke in term born children: neuroimaging predictors, clinical course and cognitive outcome. Tartu, 2024, 160 p.

366. **Allan Tobi.** Development of Smart Nanoparticles for Experimental Treatment of Cancer. Tartu, 2024, 160 p.