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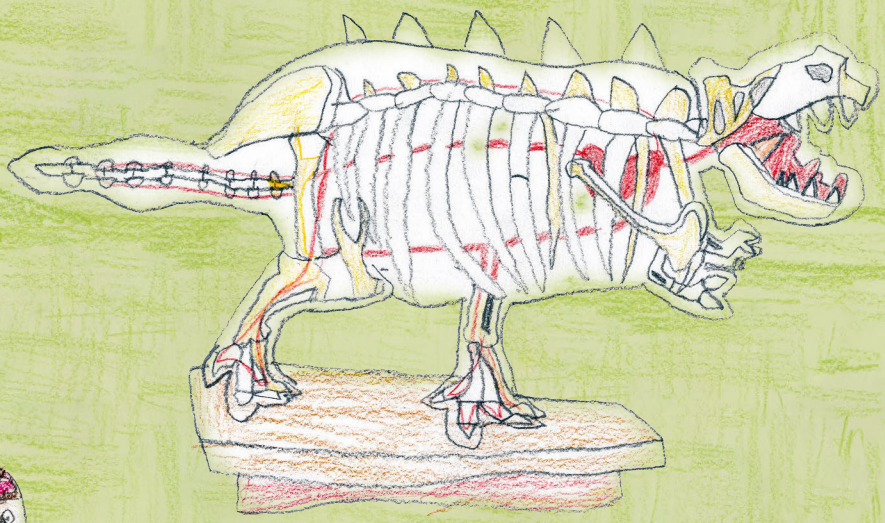
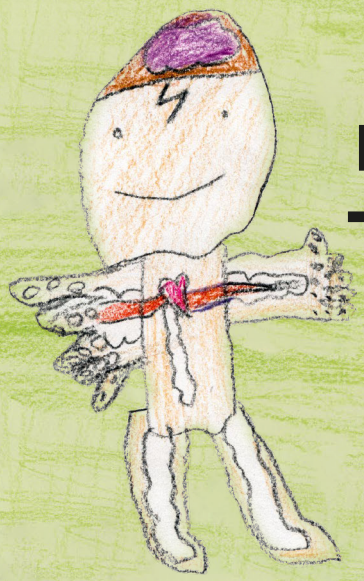


How Can Laboratory Parameters Aid Clinicians in Prediction of Cardiovascular Events, Institutionalization and Mortality in Older People?

Elisa Heikkilä



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SARJA – SER. D OSA – TOM. 1957 | MEDICA – ODONTOLOGICA | TURKU 2026

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UNIVERSITY OF TURKU
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ELISA HEIKKILÄ: How can laboratory parameters aid clinicians in prediction of cardiovascular events, institutionalization and mortality in older people?
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ABSTRACT

Background: Cardiovascular diseases are the most common cause of death worldwide, and a major cause for disability and mortality in older people. Laboratory parameters can be of aid in predicting cardiovascular events and mortality. Indexes that combine different parameters can help in risk prediction. Many previous indexes include a large number of clinical and/or laboratory parameters, which complicates their use in clinical practice.

Aims: The aim of the thesis was to study how a combination of routine laboratory parameters can be used to estimate an older individual's risk for institutionalization and mortality. Also, the aim was to study how cardiac markers troponin T (cTnT) and N-terminal pro-brain natriuretic peptide (proBNP) can estimate both cardiovascular outcomes and all-cause mortality, and how the concentrations of these markers change with ageing.

Results: Older people's mortality could be predicted with fourteen routine laboratory parameters, or a combination of six clinical and three laboratory parameters. Laboratory parameters could not predict institutionalization, but it could be predicted with three clinical parameters. Elevated concentrations of cTnT and proBNP both predict cardiac events, and cardiovascular and all-cause mortality, but their concentrations rise with normal ageing as well.

Conclusions: Only a small number of routine laboratory parameters as well as cTnT and proBNP above age-adjusted reference limits help to predict mortality in older people. On the contrary, institutionalization is associated with clinical parameters which reflect difficulties of activities in daily living.

KEYWORDS: laboratory tests, cardiac markers, mortality, institutionalization, cardiac events, older people

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
Kliininen kemia
ELISA HEIKKILÄ: Miten laboratoriokokeet auttavat lääkäriä sydän- ja verisuonitapahtumien, pitkäaikaishoidon tarpeen ja kuolleisuuden ennustamisessa?
Väitöskirja, 125 s.
Turun kliininen tohtoriohjelma
Maaliskuu 2026

TIIVISTELMÄ

Tausta: Sydän- ja verisuonisairaudet ovat yleisin kuolinsyiden ryhmä maailmanlaajuisesti, sekä merkittävä ikääntyneiden toimintakyvyn laskun ja kuolleisuuden aiheuttaja. Laboratoriokokeilla voidaan ennustaa sydän- ja verisuonitautitapahtumia ja kuolleisuutta. Eri parametreja yhdistävät indeksit voivat auttaa riskinarvioinnissa. Monet käytetyt indeksit sisältävät hyvin suuren määrän kliinisiä ja/tai laboratorioparametreja, mikä tekee niiden käytöstä kliinisessä työssä hankalaa.

Tavoitteet: Väitöskirjatyön tavoitteena oli tutkia, kuinka rutiininomaiset laboratoriokokeet voivat auttaa arvioitaessa ikääntyneen riskiä päätyä pitkäaikaishoitoon tai kuolla. Lisäksi tavoitteena oli selvittää, kuinka sydänmerkkiaineet troponiini T (cTnT) ja b-tyypin N-terminaalinen natriureettinen propeptidi (proBNP) ennustavat sekä sydän- ja verisuonitapahtumia että kuolleisuutta, sekä kuinka näiden merkkiaineiden pitoisuudet muuttuvat ikääntymisen myötä.

Tulokset: Ikääntyneiden kuolleisuutta voitiin ennustaa neljällätoista rutiinikäytössä olevalla laboratorioparametrilla, tai kuuden kliinisen ja kolmen laboratorioparametrin yhdistelmällä. Laboratorioparametreilla ei voitu ennustaa pitkäaikaishoitoon päätymistä, mutta sitä voitiin ennustaa kolmella kliinisellä parametrilla. cTnT:n ja proBNP:n kohonneet pitoisuudet ennustivat sydän- ja verisuonitapahtumia sekä kuolleisuutta niin sydänsairauksiin kuin muihinkin syihin, mutta niiden pitoisuudet nousivat myös normaalin ikääntymisen myötä.

Johtopäätökset: Pieni määrä rutiinikäytössä olevia laboratoriokokeita samoin kuin iän mukaiset viitearvot ylittävät cTnT- ja proBNP –pitoisuudet auttavat ikääntyneiden kuolleisuuden ennustamisessa. Sen sijaan pitkäaikaishoitoon päätyminen on yhteydessä kliinisiin parametreihin, jotka heijastavat päivittäistoiminnoista selviytymistä.

AVAINSANAT: laboratoriokokeet, sydänmerkkiaineet, kuolleisuus, pitkäaikaishoito, sydäntapahtumat, ikääntyneet

Table of Contents

Abbreviations

ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMI	Acute myocardial infarction
AUC	Area under the curve
CI	Confidence interval
CRP	C-reactive protein
cTnT	Cardiac troponin T
CV	Cardiovascular
CVD	Cardiovascular disease
ECLIA	Electrochemiluminescence immunoassay
FI	Frailty index
HDL	High-density lipoprotein
HR	Hazard ratio
ICD-10	10^{th} Revision of International Statistical Classification of Diseases and Related Health Problems
IQR	Interquartile range
LDL	Low-density lipoprotein
LI	Laboratory index
LoD	Limit of detection
LoQ	Limit of quantitation
NPV	Negative predictive value
PPV	Positive predictive value
proBNP	N-terminal natriuretic b-type propeptide
SD	Standard deviation
TSH	Thyroid stimulating hormone

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Heikkilä E, Salminen M, Viljanen A, Katajamäki T, Koivula MK, Pulkki K, Isoaho R, Kivelä SL, Viitanen M, Löppönen M, Vahlberg T, Viikari L, Irjala K. A practical laboratory index to predict institutionalization and mortality - an 18-year population-based follow-up study. *BMC Geriatrics* 2021 Feb 25;21(1):139. doi: 10.1186/s12877-021-02077-1.

II Heikkilä E, Salminen M, Viljanen A, Katajamäki T, Koivula MK, Pulkki K, Isoaho R, Kivelä SL, Viitanen M, Löppönen M, Vahlberg T, Venäläinen MS, Elo LL, Viikari L, Irjala K. A novel easy-to-use index to predict institutionalization and death in older population - a 10-year population-based follow-up study. *BMC Geriatrics* 2023 Feb 7;23(1):80. doi: 10.1186/s12877-023-03760-1.

III Heikkilä E, Katajamäki T, Salminen M, Irjala K, Viljanen A, Koivula MK, Pulkki K, Isoaho R, Kivelä SL, Viitanen M, Löppönen M, Vahlberg T, Viikari L. New reference limits for cardiac troponin T and N-terminal b-type natriuretic propeptide in elders. *Clinica Chimica Acta* 2024 Mar 15;556:117844. doi: 10.1016/j.cca.2024.117844.

IV Heikkilä E, Katajamäki T, Salminen M, Irjala K, Viljanen A, Koivula MK, Pulkki K, Viitanen M, Vahlberg T, Viikari L. High-sensitivity cardiac troponin T and N-terminal b-type natriuretic propeptide are associated with cardiac and all-cause mortality in older adults - A population-based ten-year follow-up study. *Clinica Chimica Acta* 2025 Feb 1;567:120116. doi: 10.1016/j.cca.2024.120116.

1 Introduction

The average lifespan is increasing. The world's population is expected to continue to grow over the coming decades, until reaching a peak of over 10 billion people in the 2080s. By then, the number of over 65-year-olds is estimated to surpass the number of under 18-year-olds, being over 2 billion (United Nations, 2024). Developments in medical treatments and new medicines and advances in medical technology and improvements in the access to health care have contributed in global population ageing and at the same time increased the prevalence of chronic diseases. The challenge of ageing research is to find ways to increase healthy lifespan. While the average lifespan has increased, the percentual time lived with disability has not decreased. Thus, the absolute number of years lived with disability has even grown and was estimated to be nine years in 2020 (World Health Organization, 2024). The aim should be to compress morbidity to less years lived with disability (Garmany et al., 2021). With more disease-free and functional additional years, it could be possible to improve survival at home and the quality of life in later years.

Persons at the same chronological age can have very different functional and cognitive capacities (Mitnitski et al. 2002). On average, organ system functions decline with age, but the rate varies, within and between individuals, also in people who are otherwise well. There is a tendency towards more personalized health care, where treatment could be more optimized and targeted to the individual. Multiple factors contribute to the individual rate of ageing some of which can be modified by medical interventions or personal habits of life. Much is already known about healthy life habits that prevent declining of physical condition such as healthy nutrition and adequate physical exercise. Also, social and mental factors are known to contribute to healthy ageing. One way to estimate a person's state of health and susceptibility to adverse health risks is to calculate an index score that combines clinical or laboratory defects that an individual possesses. This kind of an index can be called a frailty index (FI). Often these indexes contain a large number such as over thirty clinical and/or laboratory parameters. Various FIs have been used to predict older people's health risks and mortality. It has been proposed that a person's biological age could be estimated by comparing their FI score with the average FI score at their age. As frailty predicts adverse effects better than

chronological age, it may serve as a proxy measure of biological age (Mitnitski et al., 2001, 2002; Clegg et al., 2013).

Ageing is the largest risk factor for cardiovascular disease (CVD) (North & Sinclair, 2012). On the other hand, maintaining cardiovascular (CV) health is essential for the whole organism. Normal circulatory function is an important factor in determining the whole organism's longevity. Throughout lifespan, the CV system is under constant mechanical and metabolic stress (Abdellatif et al., 2023). Nevertheless, while many people acquire CV and other diseases by old age, there are also many who achieve old age without evidence of these diseases. There are typical age-related changes seen in cardiac function, but some still preserve good performance in the old age (Lakatta, 2002). People have often developed many comorbidities and risk factors for CVD by old age. The prevalence of pathologies that affect the CV system is still growing, and they are the leading cause of global morbidity, disability and mortality (Abdellatif et al., 2023), resulting in 40 percent of deaths in over 65-year-olds, and the cost associated with treatment is also still increasing (Fleg et al., 2011; North & Sinclair, 2012). Prevention and early detection of CVD is crucial so that treatment, including counselling and medication, can start promptly. There is evidence on the benefits of treating CV risk factors also in older age (Bulló et al., 2011; Yang et al., 2021; Lam et al., 2007).

CVD risk is traditionally assessed with models that include known risk factors for CVD: high blood pressure, cigarette smoking, dyslipidemia, obesity and diabetes, some also include the elevated risk with higher age and male gender. Many models include some laboratory values such as cholesterol levels. The role of the risk factors may change in older age, and the traditional risk evaluation methods may not perform well especially in primary prevention in older population. Measuring levels of CV biomarkers could improve the accuracy of risk stratification especially in individuals with an intermediate risk score and potentially lead to more intensive preventive strategies to those with elevated biomarker levels. The demand for more precise risk assessment methods continues to grow as newer, costly medications are introduced into clinical practice, and more diverse treatments for CVD prevention are available.

Therefore, the focuses of this thesis were to study how the concentrations of cardiac biomarkers change with age, and how they could be used in risk prediction, and to study the possibilities to predict risks for overall mortality and institutionalization with a combination of a small number of parameters.

2 Review of the Literature

2.1 Ageing population

Older population is a diverse group of individuals with different backgrounds, and in different states of health and physical condition. In addition to physical age, the biological age of older people varies. Older population can be defined as 65-year-olds and older (Organisation for Economic Co-operation and Development, n.d.). The proportion of over 65-year-olds is growing worldwide (United Nations, 2024), and in Finland (Figures 1, 2 and 3; Official Statistics Finland, 2024). While many over 65-year-olds are still in a good condition, it is noteworthy that also the number of over 75- and over 85-year-olds has grown and is estimated to continue to grow rapidly (Figure 3). The proportion of 65-year-olds and older in Finland was 7.3 in 1960, and has grown each year, being 22.6 in 2020, and 23.6 in 2024. Only 0.1 percent of the population in Finland were aged 85 years or over in 1950, and their percentage has grown to 3.0 percent in 2024 (Official Statistics Finland, 2025).

Both the average expected life span has increased worldwide as well as healthy life expectancy. Life expectancy increased globally by more than 6 years between 2000 and 2019, being 73.1 years in 2019. Healthy life expectancy increased by 5.4 years during the same period, from 58.3 in 2000 to 63.7, in 2019. As the increase seen in healthy life expectancy is not quite as large as the increase in life expectancy (5.3 years vs 6.4 years), this means that there was no decrease in the years lived with disability. The prevalence of many diseases increases with advancing age. The COVID-19 pandemic reversed the increase in both life expectancy and healthy life expectancy, both retreating to 2012 levels in 2021 (71.4 years and 61.9 years, respectively). (World Health Organization, 2024.)

The increasing older population, with no reduction in the years lived with disability, creates a grand challenge to health care systems worldwide. Considering the costs of institutionalization, there is a tendency and a necessity to reduce institutional care and enable old people to live at home longer with home care. This is problematic since the resources are scarce and not all old people in home care are in a healthy enough cognitive or physical condition to live alone.

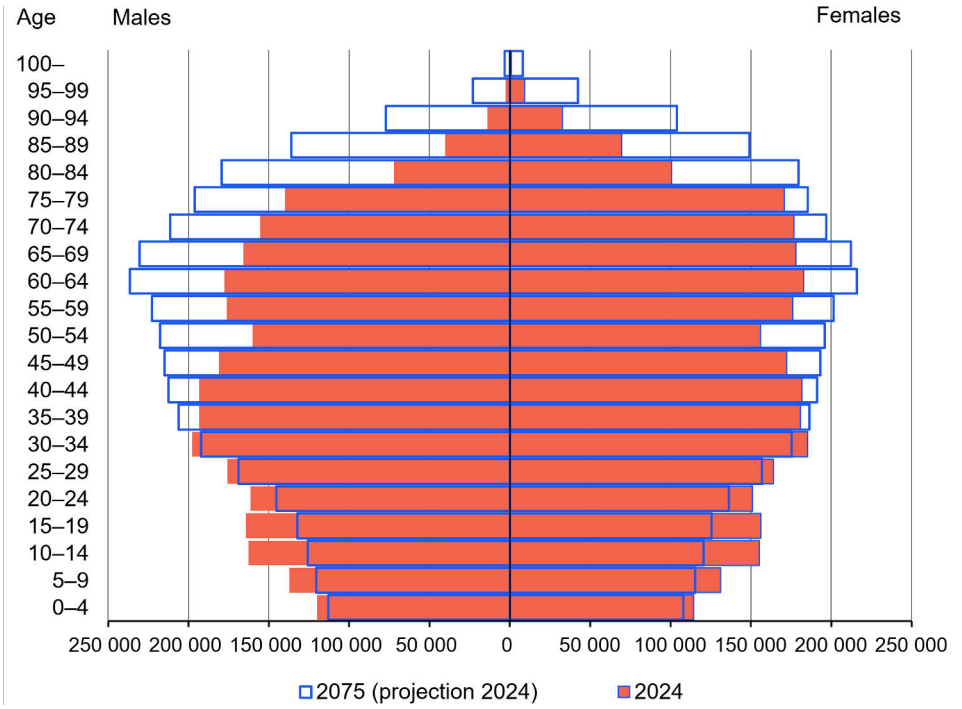


Figure 1. Age structure of population by age group and gender in Finland 31.12.2024 and 2075, projection 2024. Source: Official Statistics Finland [referred: 27.8.2025] Access method: https://stat.fi/en/statistics/vaenn. Reprinted according to the Creative Commons Attribution 4.0 International License.

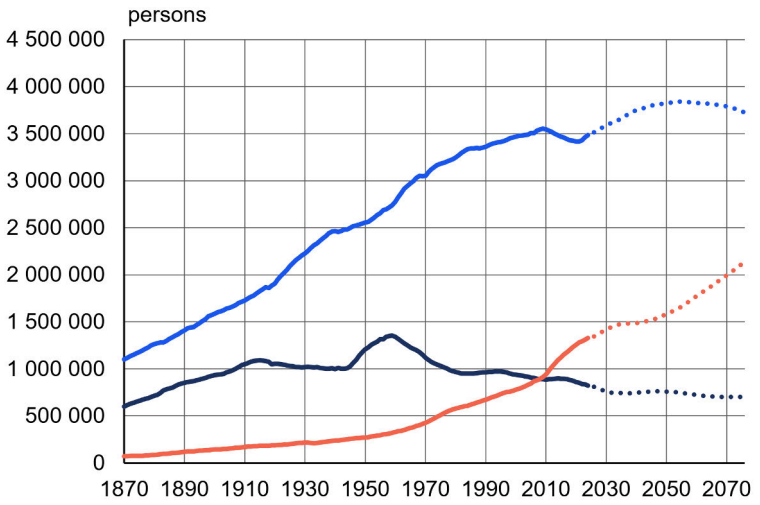


Figure 2. Population 1870–2024 and population projection 2025–2075 in Finland by age group, under 15-year-olds indicated by black line, 15 to 64-year-olds by blue line, and 65-year-olds and older by red line. Source: Official Statistics Finland [referred: 27.8.2025] Access method: https://stat.fi/en/statistics/vaenn. Reprinted according to the Creative Commons Attribution 4.0 International License.

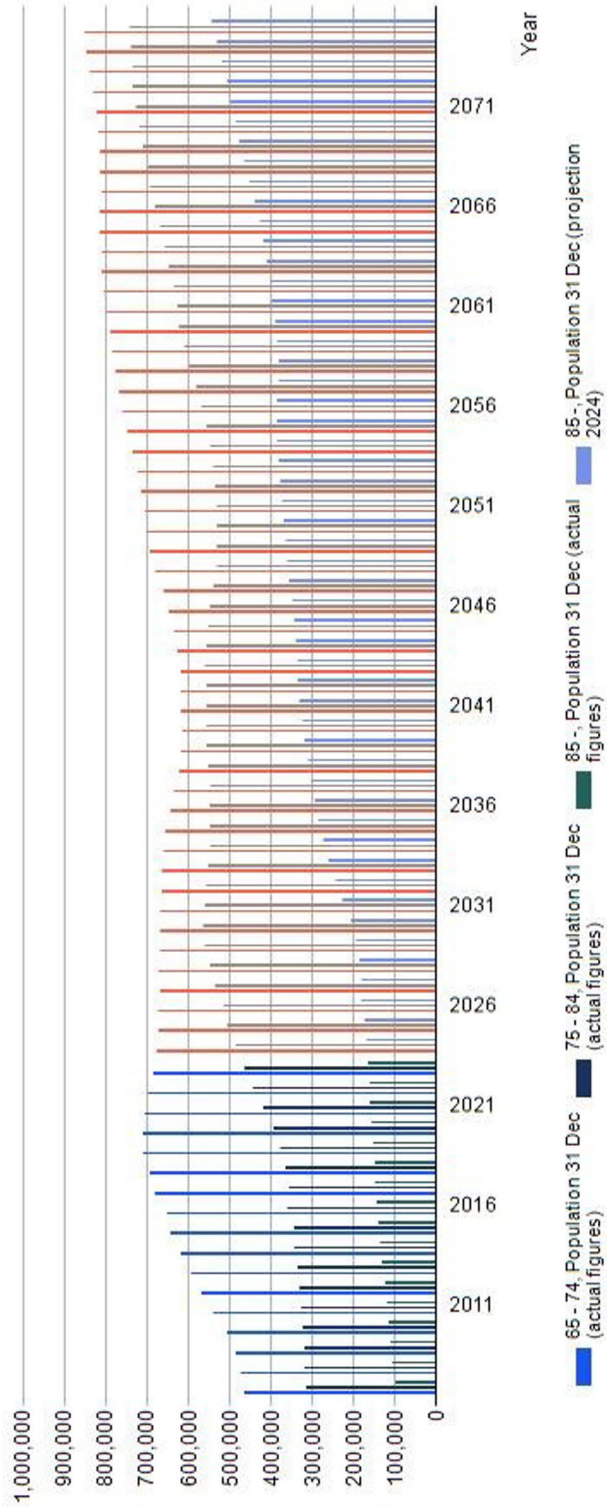


Figure 3. Over 65-year-old population 2007–2024 and population projection 2025–2075 in Finland by age groups 65–74, 75–84 and 85–. Created from data of Official Statistics Finland [Referenced: 4.11.2025]. Data access method: https://pxdata.stat.fi PXWeb/pxweb/en/StatFin/.

2.2 Cardiovascular ageing

Numerous physiological processes decline with age which leads to an increased risk of disease (Abdellatif et al., 2023). It is not always clear which symptoms or features are part of a normal ageing process, and which are due to a pathological condition.

Ageing has a major effect on the heart and arterial systems leading to an increase in CVDs including atherosclerosis, hypertension, myocardial infarction, and stroke (Lakatta & Levy, 2003; North & Sinclair, 2012). There are different proposed mechanisms about why the prevalence of CVDs increases with advancing age.

In addition to extrinsic stress, organisms face constant intrinsic stress such as reactive oxygen species produced by metabolism. Cell senescence leads to the loss of replicative capacity and deterioration of cell components and cellular functions. These factors inevitably cause accumulation of damage, leading to alterations in the homeostasis of tissues and eventually the whole organism (Vicencio et al., 2008). Also misfolded and damaged proteins and mutations accumulate with age (Abdellatif et al., 2023). There are multiple repair mechanisms responding to damage such as telomerase enzyme that repairs chromosomal damage. Telomerase activity seems to be one factor involved in determining longevity (Nicholls et al., 2011). Clearance mechanisms such as autophagy are important as well, and especially in terminally differentiated cells like cardiomyocytes (Kirkwood, 2011; Vicencio et al., 2008). Limitations in repair mechanisms lead to age-related pathologies and declining health over time (Vicencio et al., 2008).

The heart undergoes characteristic changes also in individuals without a CVD. The still partly unknown genetic pathways that regulate ageing, also influence CV ageing (Lakatta & Levy, 2003; North & Sinclair, 2012). Mitochondrial function declines with age in most tissues, and this ageing affects also myocardial cells that are long-lived cells rich in mitochondria and a high demand of energy (North & Sinclair, 2012). The ageing process changes CV structure and function which enhances the risk for pathophysiological disease mechanisms. The complex interactions involve age, multiple risk factors, and genetics (Lakatta & Levy, 2003; Abdellatif et al., 2023).

Some pathological alterations of the heart include hypertrophy, alterations in the left ventricular diastolic function and systolic capacity, increased arterial stiffness, and impairment of the endothelial function (Abdellatif et al., 2023; Lakatta & Levy, 2003). The health of the arterial and cardiac systems is linked. Myocardial hypertrophy and fibroblast proliferation can be compensatory mechanisms for increasing arterial stiffness. The number of cardiac myocytes decreases with age, which causes additional load due to stretching of the cells that remain. The increase in the size of the remaining myocytes and in the amount of collagen thickens the left ventricle wall (Gazoti Debessa et al., 2001). Also, the atrial size increases in otherwise healthy aged people, and the secretory behavior of the myocytes alters so that, for example, the secretion of

atrial natriuretic peptides is increased (Lakatta, 2002). These changes result in decreased cardiac output and increase in the amount of fibrotic tissue (Lakatta & Levy, 2003). Structural changes of the heart, including fibrosis and hypertrophy, slow propagation of electric impulse throughout the heart. The number of cells in the sinoatrial node decreases influencing heart rate. These age-related changes decrease both rate variability and maximum heart rate (Antelmi et al., 2004).

All these changes reduce the compensatory capacity of the aged heart and make the heart more prone to myocardial dysfunction and failure (Olivetti et al., 1991). Cardiomyocytes are renewed at a very slow pace of approximately 1% per year at the age of 20, and 0.3% at the age of 75. Myocardial cells still have some regenerative potential as the rate of renewal of cardiomyocytes can increase after myocardial damage (Bergmann et al., 2009).

While ageing increases the prevalence of CVDs, it has been speculated that CV ageing might precede or underlie age-related deterioration of overall health. The function of the CV system is vital in preserving the overall health as it provides blood circulation delivering oxygen and nutrients to all tissues, including the muscle and the brain (Abdellatif et al., 2023).

2.3 Risk factors for cardiovascular disease

2.3.1 Conventional risk factors

The most important known traditional risk factors for developing CVD besides age and male gender include high blood pressure, cigarette smoking, dyslipidemia, obesity and diabetes, that account for approximately half of the global burden of CVD (The Global Cardiovascular Risk Consortium, 2025; Magnussen et al., 2023). Risk scores that combine these factors to assess an individual's likelihood of experiencing adverse CV outcomes have been developed; some considering additional factors such as medication use or geographical region. While age and gender are non-modifiable risk factors, they aid in understanding the overall risk. They are commonly included in risk-prediction models that are used in tailoring prevention (Conroy et al., 2003; D'Agostino et al., 2008; Wilson et al., 1998).

Compared to risk scores designed for the general adult population, some differences are expected when estimating risks in older population. Conventional risk prediction models often do not consider the competing risk of death from non-CV causes, which may lead to overestimation of the benefits of risk factor treatment in older persons. A modified risk score for older people over the age of 70 has been developed as the relationship between traditional risk factors and CVD attenuates with age. (SCORE2 working group and ESC Cardiovascular risk collaboration,

2021; SCORE2-OP working group and ESC Cardiovascular risk collaboration, 2021; Neumann et al., 2025.)

2.3.2 Non-traditional markers for cardiovascular risk

The discriminatory value of most CV risk scores is moderate (Neumann et al., 2025). Emerging risk factors and biomarkers that are not part of traditional risk models but have been demonstrated to be independently linked to CV risk are gaining evidence for their ability to offer additional insights beyond traditional risk factors. Factors that have been studied are high-risk ethnicities, unfavourable body composition, presence of chronic inflammatory conditions, chronic kidney disease, genetic data, CV imaging results and circulating biomarkers (Neumann et al., 2025; Wang et al., 2023). Some of the biomarkers that could potentially enhance the accuracy of CV risk prediction reflect conditions that predispose the person to develop a CVD. C-reactive protein (CRP) and fibrinogen, markers for inflammation, and creatinine and cystatin C, markers for impaired kidney function, are associated with CVD (The Emerging Risk Factors Collaboration, 2012; Perone et al., 2025). Also, low and high alanine aminotransferase, high homocysteine levels and hyperuricemia have been found to be associated with increased CV mortality (Gospodarczyk et al., 2022; Moshkovits et al., 2024; Ndrepepa & Kastrati, 2019; Wang et al., 2023). Still, the incremental value of biomarkers when added to established risk models is modest. The identification of new biomarkers and optimal target populations may enhance their value in risk prediction in the future (Neumann et al., 2025).

There are also newer biomarkers related to lipid metabolism. Lipoprotein (a) is a genetically determined lipoprotein variant with atherogenic and prothrombotic properties linked to the risk of CVD. European guidelines have suggested its measurement at least once for each person (Perone et al., 2025; Visseren et al., 2021).

More recently, another class of lipids called ceramides has been recognized to predict CV end points. Risk scores based on ceramide levels could be used as efficient risk stratifiers in both primary and secondary prevention of atherosclerotic CVD, but their measurement requires specialized analytics (Katajamäki et al, 2022; Hilvo et al., 2020).

CV biomarkers, including cardiac troponins and natriuretic peptides, can also be used to classify CV risk, especially in individuals at intermediate risk (Neumann et al., 2025). The role of troponins and natriuretic peptides in long-term risk prediction for CV events and mortality is discussed later in more detail.

2.3.3 Cardiovascular risk factors in old age

Most CV risk factors, not including age and gender, can be controlled by addressing behavioral factors such as an unhealthy diet, obesity, and physical inactivity. In older adults, advancing age is the predominant CV risk factor. Older people are underrepresented in primary and secondary prevention trials, and especially those who have comorbidities or are frail (Abrigani et al., 2024). There is some evidence on the benefits of addressing risk factors still in older age, although the role of risk factors differs from younger age groups (Bulló et al., 2011; Makino et al., 2021; Yang et al., 2021; Vilela de Sousa et al., 2023; Abrigani et al., 2024).

Obesity may not be a similar risk factor in the older population as in younger population, but in younger old age (before the age of 70) moderate weight loss may still be beneficial in overweight older people to reduce their risk for diabetes, CVDs and mobility difficulties. In older population, the risk for total mortality caused by obesity is smaller than the risks caused by unintentional weight loss. (Strandberg et al., 2013; Suominen et al., 2014.)

Type 2 diabetes mellitus significantly increases the risk of CVD. In high-income countries, individuals with diabetes face, on average, a twofold higher likelihood of developing CVD outcomes compared to those without diabetes (Pennells et al., 2023; Sarwar et al., 2010). Diabetes and hyperglycemia increase total and CV mortality. The earlier the person's age at the onset of diabetes, the greater its effect on total and CV mortality (Abdelhafiz & Sinclair, 2022; Kaptoge et al., 2023; Morley et al., 2004). A study in an older population found metabolic syndrome strongly associated with CVD risk, and on the other hand higher weight was associated with the risk for metabolic syndrome. In this study, the older obese individuals without metabolic syndrome did not have a higher risk for CVD and concluded that targeting cardiometabolic risk factors could be considered in older people, regardless of weight status (Dhana et al., 2016). Many CV risk factors are closely connected. Obesity is associated with the risk for metabolic syndrome and lower physical activity, which are all risk factors for CVD (Dhana et al., 2016; Yang et al., 2021).

A study on older men found light or vigorous physical activity to be strongly and negatively associated with CV as well as all-cause mortality. In the same study, both cessation of smoking and increasing physical activity even in old age reduced mortality (Holme & Anderssen, 2015). Cigarette smoke accelerates the development of atherosclerosis by enhancing oxidation of lipids, thrombosis, inflammation, arterial stiffness, and endothelial dysfunction (Ambrose & Barua, 2004). Smoking is a well-known risk factor for CVD and mortality in general population, and there is some evidence of the benefits of the cessation of smoking also in old age although the excess risk of smoking may be less apparent in the oldest old where smokers are increasingly strongly selected survivors (Lam et al.,

2007), and because the benefits might not be achieved during the first years after quitting smoking (Wei et al., 2021).

Total cholesterol and low-density lipoprotein (LDL) cholesterol are risk factors for all-cause and CV mortality in general population (Stamler et al., 1999), but evidence regarding the effects of ageing on total and LDL cholesterol levels, and their role as risk factors for CVD and mortality is controversial (Bertolotti et al., 2024; DiNicolantonio & McCarty, 2018). Their levels may rise in older middle age and younger old age but decline with very old age, as well as with chronic disease, inflammation, malnutrition, or poor health status in older persons. In older population, especially in the oldest old, low total cholesterol, and possibly also low LDL cholesterol, may be associated with increased mortality (Nanna et al., 2019; Ravnskov et al., 2016; Schupf et al., 2005; Tikhonoff et al., 2005). An increased cholesterol level still seems to indicate an increased risk for ischemic heart disease mortality also in older populations (McMahon et al., 2007). In another study on our population, the highest age quartile had the lowest total and LDL cholesterol levels, presumably due to general frailty and decreased protein synthesis, and both total and LDL cholesterol had statistically significant predictive ability in primary prevention of atherosclerotic CVD only in men and not in the oldest quartile (Katajamäki et al., 2025). LDL cholesterol may lose its predictive ability in primary prevention in older age, but a meta-analysis showed that lowering LDL cholesterol with medications reduced the risk for major CV events in over 75-year-olds at least as well as in younger adults, especially in secondary prevention (Gencer et al., 2020). Studies have found statin therapy beneficial in older population in secondary prevention of atherosclerotic CVD at least until the age of 80 years and safe as long as recommendations for this population are followed, but side effects may occur more frequently than in the younger population (Félix-Redondo et al., 2013; Bertolotti et al., 2024).

Blood pressure is another risk factor whose role may differ in older population compared to younger adult population. Blood pressure rises with age mainly due to increased arterial stiffness. Almost one third of adults worldwide are estimated to have hypertension, and even over 60% of older population (Mills et al., 2016). Hypertension is an independent, strong and direct risk factor for CVD in adult population, and in large epidemiological studies it remains associated with vascular and overall mortality also in old age. High blood pressure is a complex and heterogeneous condition, and older population is also very heterogeneous, which emphasizes the need for individual consideration of the benefits of the treatment of high blood pressure (Lewington et al., 2002).

2.4 Reference intervals

2.4.1 Defining reference intervals

Clinicians determine whether an individual's laboratory measurement falls within a normal range based on reference intervals. A reference interval provides a range of acceptable values for a certain analyte (Clinical and Laboratory Standards Institute, 2010). A reference interval is formed by taking an adequate sample from the chosen reference population and defining the intervals so that 95 percent of the values fall within the reference interval.

The reference intervals vary in different populations depending on many factors such as age and ethnicity. Also habits of life in the population such as diet and exercise may impact the values in a population. The reference intervals are applied also on people with comorbidities even though reference intervals are usually defined in a healthy population. Also, the methods used in a certain laboratory produce variation in the values. If a laboratory does not define its own reference interval for a certain laboratory analyte but uses the reference interval defined in another population, they should at least verify the reference interval by collecting a sample of reference individuals from their population (Clinical and Laboratory Standards Institute, 2010; Horn & Pesce, 2003).

2.4.2 Older people’s reference intervals

Many laboratory values differ in older population from the values on general adult population. Applying reference ranges defined for general adult population may cause overdiagnosis for older population and can lead to treating normal conditions as pathological. The problem has been recognized in various laboratory parameters, and for some such as N-terminal b-type natriuretic propeptide (proBNP) and thyroid hormones there are separate reference ranges according to age. (Fradley et al., 2011; Goudot et al., 2021; Jansen et al., 2024; Nadrowski et al., 2013; Ni et al., 2022.)

The reasons for the change seen in various biomarkers with age are not always clear but physiological changes in different organ systems likely change concentrations of some analytes. This natural adaptation should not be considered as pathological (Bech et al., 2017; Duntas, 2021; Gauthier et al., 2020; Mammen, 2019). It is not always clear whether the change seen in laboratory values is due to the normal ageing process or age-related increase in the prevalence of pathologies. Evaluating the distributions of the values may aid in determining whether there is a subpopulation with differing values, which could implicate a need for a separate reference interval for a certain age group. The older the population is, the less there are individuals with no diseases which complicates defining the reference intervals

for older people, and it may be unrealistic to find a healthy reference population in older age groups (Rifai et al. 2018).

2.5 Cardiac markers

2.5.1 Cardiac troponins

Cardiac troponins regulate the contraction of striated muscle in the heart. Cardiac troponin T (cTnT) along with cardiac troponin I are expressed specifically by the heart, and they are released from the myocardium when myocytes are damaged which may occur due to a variety of reasons including inflammation, necrosis, or trauma (Askin et al., 2020; Cardinaels et al., 2015; de Lemos et al., 2010; Franzini et al., 2015; Reiter et al., 2011; Wu et al., 2018; Xu et al., 2013). Troponin concentrations may be measured in the peripheral blood in ischemic conditions such as myocardial infarctions and coronary artery disease (de Lemos et al., 2010; Reiter et al., 2011) but also in non-ischemic acute and chronic heart diseases such as left ventricular hypertrophy and heart failure (Aimo et al., 2018; de Lemos et al., 2010; Latini et al., 2007; Wu et al., 2018). Also, chronic kidney disease may increase their concentrations (Askin et al., 2020; Cardinaels et al., 2015; de Lemos et al., 2010; Franzini et al., 2015; Wu et al., 2018; Xu et al., 2013).

Cardiac troponins are mainly used for diagnosing or ruling out an acute myocardial infarction or injury (AMI). The diagnosis of an infarction requires the detection of an elevated cardiac troponin value above the 99th percentile upper reference limit. The infarction is considered acute when there is a rise or fall of troponin values indicating a newly detected dynamic state whereas in chronic infarction the troponin concentrations are persistently elevated (Thygesen et al., 2018).

Cardiac troponins T and I are the preferred biomarkers for the evaluation of myocardial injury (Thygesen et al., 2007, 2018). Other biomarkers for myocardial injury such as creatine kinase MB isoform are not as sensitive and less specific for myocardial muscle (Goodman et al., 2006).

While in younger adults troponin concentrations cannot be measured in a normal state, older people may have detectable concentrations of troponins in peripheral blood without an acute ischemic event. A number of studies show that the level of cTnT increases with age (Cardinaels et al., 2015; de Lemos et al., 2010; Franzini et al., 2015; Li et al., 2015; Menacer et al., 2013; Olivieri et al., 2012; Reiter et al., 2011; Wu et al., 2018; Zhang et al., 2020). The cut-offs used in clinical practice are not based on older population that is highly prevalent in emergency care and other health care appointments.

Many studies have found that elevated levels of cTnT are associated with CV and all-cause mortality in general and older populations with or without cardiac

disease (de Lemos et al., 2010; Devereaux et al., 2012; Latini et al., 2007; Neumann et al., 2024, Wu et al., 2018; Xu et al., 2013). Elevation of cTnT was significantly associated with increased all-cause and CV mortality in the US National Health and Nutrition Examination Survey, independently of traditional risk factors, both in non-diabetic and prediabetic individuals. The risk of CVD was even higher in those individuals with both elevated cTnT and prediabetes (Liu et al., 2023). Also, perioperative measurement of cardiac troponins could be used to evaluate a person's preoperative and postoperative risk when undergoing a noncardiac surgery (Gualandro et al., 2018; Wolfgang, 2013).

2.5.1.1 Troponin assays

High-sensitivity troponin assays are recommended and increasingly used (Mair et al., 2018; Thygesen et al., 2018). The high performance of sensitive assays has improved the early diagnosis of myocardial infarctions as they enable cardiac troponin measurement with a high degree of analytical sensitivity and a low level of analytical imprecision at the lower measuring range (Reichlin et al., 2009; Reiter et al., 2011; Thygesen et al., 2012). The increase in the early diagnostic sensitivity of high-sensitivity cardiac troponin assays reduces their specificity for AMI. With the low analytical detection limit of high-sensitivity assays, concentrations of cardiac troponins can be measured in a significant proportion of healthy adults as well, and in most older individuals (Reichlin et al., 2009). Also, more troponin elevations not caused by acute ischemia are detected than with previous less sensitive troponin assays (Mair et al., 2018).

2.5.2 N-terminal b-type natriuretic propeptide

Natriuretic peptides are secreted from cardiomyocytes in response to increased wall tension reflecting increased intravascular volume. They promote vasodilatation and regulate salt and water handling (Epstein et al., 1998; Martinez-Rumayor et al., 2008). Natriuretic peptides including proBNP are used for diagnosing and monitoring heart failure (Ponikowski et al., 2016; Taylor et al., 2017). Their concentrations rise in left ventricular dysfunction, but elevated concentrations may also be due to other conditions such as renal impairment or atrial fibrillation (Raymond et al., 2003; Taylor et al., 2017). A background of CVD and especially previous myocardial heart infarction makes heart failure more likely. Natriuretic peptides have important functions in the kidney as they increase renal blood flow and glomerular filtration rate (Volpe, 2014). The increased circulatory blood volume in patients with a chronic kidney disease causes elevation of blood pressure which together with arterial stiffness may lead to cardiac hypertrophy and heart

failure and thus contribute to the elevation in proBNP. The elevation of proBNP in patients with renal failure is partly due to the increased cardiac secretion of proBNP, and partly due to the impaired clearance from the kidneys (Okamoto et al., 2019).

Studies have shown that the concentration of proBNP is a predictor of CV events and mortality in general population (Wang et al., 2004), and of future risks in patients with an existing condition such as the risk of mortality after an AMI (Wang et al., 2023), mortality in patients with acute heart failure (Wang et al., 2020) and even stroke risk after a transient ischemic attack (Rodríguez-Castro et al., 2020). There is evidence of the prognostic value of proBNP for CV events on patients in long-term geriatric care (Sheikh Rezaei et al., 2019) and in general older population (Kistorp et al., 2005). The prognostic value of proBNP for mortality after AMI remains even in the oldest patients (Lorgis et al., 2009). The Atherosclerosis Risk in Communities Study found that proBNP could predict all-cause mortality as a single biomarker equally well in non-diabetic older adults as the Pooled Cohorts Equation that includes clinical variables and HDL and total cholesterol, and even better than the equation in diabetic older adults (Wijkman et al., 2022).

The concentration of proBNP increases with age (Costello-Boerrigter et al., 2006; Fradley et al., 2011; Galasko et al., 2005; Goudot et al., 2021; Lorgis et al., 2009; Nadrowski et al., 2013). Specific cut-offs to rule-in or rule-out acute heart failure in different age groups have been developed and are widely applied (Januzzi et al., 2006). The selected threshold value has a significant impact on the proportion of results that are considered elevated.

2.6 Frailty

Frailty is a syndrome defined as a loss of resources in several domains leading to increased vulnerability to stressors (Clegg et al., 2013; Fried et al., 2001; Pialoux et al., 2012; Rockwood & Mitnitski, 2007). It is considered a multidimensional and complex syndrome including not only physical but also cognitive, social, and psychological domains. When defining the state of frailty of a person, different aspects of health must be considered together. Fried described frailty as a phenotype consisting of five dimensions including unintentional weight loss, weakness, exhaustion, slow gait and low physical activity (Fried et al., 2001). Frailty can also be understood as accumulation of deficits (Rockwood & Mitnitski, 2007). The recovery time increases as people age which increases their vulnerability to stressors, leading to a higher prevalence of frailty (Mitnitski & Rockwood, 2016). There is individual variability in deficit accumulation that modifies the risk for adverse events and death for people of the same age (Rutenberg et al., 2018). At the individual level, the rate of deficit accumulation depends on changes in environmental stresses and variations in the time it takes to recover from stressors (Mitnitski & Rockwood,

2016). The state of frailty is dynamic and potentially reversible (He et al., 2025). Some risk and protective factors for frailty have been identified, and the factors may be biological, environmental, or related to lifestyle (Cohen et al., 2023). Frailty predicts adverse outcomes such as increased falls, hospitalization, morbidity, dependence, and mortality (Clegg et al., 2013; Fried et al., 2001; Hajek et al., 2018).

A link has been established between CV health and frailty. Endothelial dysfunction and atherosclerotic lesions may deteriorate circulation and promote physical and cognitive frailty. The relationship between frailty and CVD seems to be bidirectional, and the role of frailty is important when treating older CV patients (Strandberg & Nieminen, 2020). Frailty and even pre-frailty are independent risk factors for CVD (Veronese et al., 2017).

2.7 Frailty indexes

Frailty can be measured using FIs that are tools for assessing the individual condition and risk for adverse health events such as mortality, institutionalization, worsening health status, hospitalization, increased falls, morbidity, and dependence of an older person. Symptoms, signs, diseases, disabilities, medications, or laboratory measurements can be combined in an index to measure frailty. (Blodgett et al., 2017; de Vries et al., 2011; Rockwood & Mitnitski, 2007; Song et al., 2010.)

For a deficit to be included in a FI, its prevalence must increase with age but not saturate too early. As a group, the deficits must cover a range of systems (Searle et al., 2008). The quality and number of deficits vary in both clinical and laboratory-based indexes. Not all deficits are equal considering the risk they cause but even minor individual deficits that might not singly be significantly related to adverse outcomes together contribute to the person's state of frailty. The index score is calculated as the proportion of an individual's deficits in relation to the total amount of deficits chosen for the index (Blodgett et al., 2019; Clegg et al., 2015; Mitnitski et al., 2002; Morley et al., 2013; Rockwood et al., 2004; Rockwood & Mitnitski, 2007; Searle et al., 2008). A review on multidimensional FIs found 611 unique deficits that comprised the FIs with a median of 36 deficits, their number ranging from five to 72. Typically, at least 30 deficits were included. Diseases, most commonly diabetes, hypertension and heart failure, and symptoms or signs such as depression, falls and weight loss, were most used as deficits, followed by disabilities such as hearing or vision loss. Eight percent of the deficits included in the studies in this meta-analysis were abnormal laboratory values (Dlima et al., 2025). Despite the varying deficits that different FIs include, they show a consistent, sub-maximal limit of about 2/3 of the deficits that a person may have (Blodgett et al., 2017; Mitnitski et al., 2015; Ritt et al., 2017; Rockwood & Mitnitski, 2007).

FIs are mostly used for older population, although some have been shown to have predictive value also in younger population. On the other hand, at a very high age, age alone may exceed the predictive ability of a FI (Blodgett et al., 2017).

Frailty can be measured by clinical and laboratory-based indexes. The information they give is partly different. Diagnostic methods including laboratory tests are used for detecting or monitoring organ damage more precisely or before it advances and becomes clinically evident. The same applies for FIs, where the clinical parameters give information on the current health status of a person and the person's functional abilities, and abnormal results in blood tests may reflect preclinical conditions or diseases.

Typical characteristics for clinical and self-report FIs, and laboratory-based FIs are non-linearly increasing scores with age, submaximal limits and their associations with mortality. The pattern of deficit accumulation seems to be convex indicating increasing accumulation of deficits with age (Kulminski et al., 2006; Mitnitski et al., 2013, 2015; Rockwood et al., 2007). Clinical FIs have mostly found that women are more frail than men, but they seem to be more resilient to frailty and live longer (Gordon & Hubbard, 2020). The same does not seem to apply for laboratory-based FIs where there is no clear indication of a gender difference in the index scores. Some studies have found men to have higher scores than women, some the opposite or no difference between genders (Hakeem et al., 2023; Sapp et al., 2023). The reason for the paradox of women being more frail but more resilient to frailty is unclear. It has been theorised that women may be more prone to report and seek treatment for health issues than men but likely there are also biological factors involved (Gordon 2019).

2.7.1 Clinical indexes

Traditionally FIs are formed using clinical deficits. Some commonly used indexes include FRAIL scale, Rockwood's FI and PRISMA-7 (de Vries et al., 2011; Hoffmann et al., 2020; Rockwood & Mitnitski, 2007; Song et al., 2010; Thompson et al., 2020). FIs consisting of clinical variables are strongly associated with the risk of death, institutionalization, and worsening health status (Rockwood & Mitnitski, 2007; Searle et al., 2008; Salminen et al., 2019; Viljanen et al., 2021). In earlier studies on our population, clinical frailty tools have been found to be applicable screening instruments among community-dwelling older people where frailty was associated with higher mortality and institutionalization rates according to three different clinical frailty screening tools. Simple frailty tools that comprised of five to seven self-reported items were found comparable with a multidimensional and time-consuming Rockwood's FI that includes at least thirty items. The hazard ratios (HRs) for different clinical FIs for 10-year-mortality for a person defined as frail were 7.96 for Frail Scale, 5.96 for Rockwood's FI and 4.41 for PRISMA-7 in unadjusted models, and the

associations persisted after adjustments with age and gender (Salminen et al., 2019). The HRs for institutionalization in unadjusted analyses were 3.32, 8.82, and 3.95, respectively, and the associations remained statistically significant after adjustments (Viljanen et al., 2021).

2.7.2 Laboratory indexes

The idea of laboratory-based indexes is that subclinical deficits, taken together, and even including deficits not individually related to mortality, may contribute to the risk of adverse outcomes of ageing. These deficits may precede clinically evident health deficits and have predictive value even in those with little other evidence of frailty. (Blodgett et al., 2016, 2019; Collerton et al., 2012; Howlett et al., 2014; Howlett & Rockwood, 2013; Mitnitski et al., 2015; Rockwood et al., 2015.)

The ideal frailty screening tool would quantify frailty based on data that are collected routinely, and that requires minimal participation by patients. Routinely collected laboratory data would fulfill this criterion. In the first study on a laboratory-based FI by Howlett et al., data from the Canadian Study of Health and Aging was re-analyzed leading to the finding that an index based on laboratory deficits could predict mortality. In their study the HRs for mortality increased by 2.8% for each increment in their 23-item laboratory FI. (Howlett et al., 2014.)

Research on laboratory-based FIs has increased during the last decade (Hakeem et al., 2023; Sapp et al., 2023). Many studies have demonstrated that prediction of mortality and other adverse health outcomes can be based on laboratory data (Howlett et al., 2014; Rockwood et al., 2015; Blodgett et al., 2016, 2017, 2019; Ritt et al., 2017; Hao et al., 2019; Wang et al., 2022; Ellis et al., 2025). The most studied outcome in laboratory-based index studies has been mortality. In most studies, the laboratory-based indexes were associated also with other outcomes apart from mortality, including disabilities, health care use and self-reported health (Sapp et al., 2023).

The index by Howlett et al. that has been used in many studies consisted of 21 laboratory variables and systolic and diastolic blood pressure. The laboratory parameters were albumin, aspartate aminotransferase, calcium, creatinine, folate, folate in erythrocytes, fasting glucose, hemoglobin, mean corpuscular volume, alkaline phosphatase, inorganic phosphorus, potassium, sodium, thyroid stimulating hormone, thyroxine, free thyroxine, urea, vitamin B12, and white blood cell count (Howlett et al., 2014). The parameters and their number are similar in most other laboratory-based indexes. Some have formed indexes consisting of biomarkers that need specialized analytics such as Mitnitski et al. in Newcastle study in over 85-year-olds, where their index of 40 parameters included inflammatory, hematological,

immunological, cell senescence, genetic, and epigenetic markers such as telomere length, DNA repair, and DNA repair to damage ratio (Mitnitski et al., 2015).

Rockwood et al. found a strong linear relationship with a laboratory-based index and a clinical FI in a study on older adults in long-term care facilities (Pearson correlation coefficient 0.95). A laboratory-based index could identify long-term care residents at increased risk of death, and it also added to clinical information, as an index combining clinical and laboratory data showed the best predictive value (Rockwood et al., 2015), HRs for the clinical FI 1.03, the laboratory-based FI 1.02, and the combined FI 1.04 for each 0.01 increment in the corresponding FI in age- and gender-adjusted models. Blodgett et al. examined associations of a laboratory-based index and adverse health outcomes in adult population and found that higher index scores were associated with poor health outcomes at all ages (Blodgett et al., 2019). In their study on older men, the correlation between a laboratory-based index and a clinical FI was relatively weak (Pearson correlation coefficient 0.33), but HRs were similar to Rockwood et al.'s study with a slightly higher HR for the clinical FI (1.05) than the laboratory-based FI (1.04), and highest for the combined FI (1.07) for each 0.01 increment in the index score. In their study, rates of institutionalization, doctor visits, medication use, self-reported health and falls increased as each index score increased (Blodgett et al., 2016). The number of laboratory parameters was the same (23) in both studies, but the number of clinical parameters (58 and 39) was different. Blodgett et al. suggested that a laboratory-based index could be utilized as an early screening tool to identify deficit accumulation at the cellular and molecular level before they become clinically visible (Blodgett et al., 2016, 2019). A laboratory-based index has also been studied in acutely ill older adults admitted to hospital, and could be useful also in an acute setting in identifying the severity of illness of patients who are frail at presentation to hospital and for creating their early care plan (Ellis et al., 2020; Jäger et al., 2019; Klausen et al., 2017). A laboratory-based index has also been found predictive of mortality in the very old of over 90 years of age (Hao et al., 2019).

2.7.3 Combined indexes

There have been prior studies that have used both clinical and laboratory data to construct FIs (Blodgett et al., 2016, 2017, 2019; Howlett et al., 2014; Ritt et al., 2017; Rockwood et al., 2015). Combining laboratory parameters with self-reported items seems to increase their predictive value, and in most studies where a clinical FI, a laboratory-based FI, and a combination of these indexes was formed, the combined index showed the best predictive ability (Blodgett et al., 2017, 2019; Rockwood et al., 2015; Howlett et al. 2014). Still, a review on laboratory-based FIs found that combining laboratory-based FIs with non-laboratory-based FIs only marginally

increased the predictive ability in seven studies (Hakeem et al., 2023). It is unclear whether the nature of the included deficits or their number increases the predictive ability of the index, since some studies have found that adding more deficits to an FI can strengthen its predictive ability (Blodgett et al., 2019; Rutenberg et al., 2018).

2.8 Institutionalization

Institutionalization can be defined differently depending on the country, but in Finland it is considered to include long-term care in an institution, where a person is provided 24/7 assisted living.

The rate of institutionalization does not depend solely on the health status of older people themselves but is also affected by health policies. In Finland, the goal is to decrease institutional care by increasing home care to enable older people to live longer at their homes. The care needs for most older people can be met at home but because of the rapidly ageing population, it is still likely that the need for institutional care will increase as well. In addition to home and institutional care, the aim is to increase communal living, which is a lighter form of care for those with impaired function, but who are not in need of 24/7 care. Communal care includes living in a safe and suitable environment with social interactions and services available during daytime, and an individual care plan which may include home care services according to the person's needs (Ministry of Social Affairs and Health, 2024).

Due to the mentioned policies during the last decade, the number of older people in institutional care has decreased in Finland each year, with a twenty percent decrease from 2023 to 2024, being 47 583 persons at the end of year 2024. Four percent of 65-year-olds and older, seven percent of 75-year-olds and older, and sixteen percent of 85-year-olds and older were in institutional care in 2024. The number of people living in assisted or communal care has increased but is still small in comparison to institutional care with 4 529 persons at the end of year 2024 (Finnish Institute for Health and Welfare, 2025).

Progressive chronic diseases cause the most need for services including institutional care. Dementia is the leading cause of disability in old age, and it is by far the disease that most often leads to a person's need to enter long-term care. In over 90-year-old people with dementia, the odds of disability in activities of daily living were almost five-fold compared to people with three other diseases but no dementia (Vargese et al. 2023). The number of disability-adjusted life years from Alzheimer's disease more than doubled between 2000 and 2021 (World Health Organization, 2024), which contributes significantly to the need for institutional and other care plans. Other factors leading to institutional care besides dementia include multimorbidity, functional dependence, cerebrovascular disease, hip fracture and Parkinson's disease (Agüero-Torres et al. 2001; Halonen et al. 2019).

2.9 Mortality

Noncommunicable diseases have become more prominent causes of death worldwide. CVD is the biggest group of noncommunicable diseases, and caused 19.2 million deaths in 2021, which is 32 percent of all global deaths, followed by malignant neoplasms that caused 9.8 million deaths. Over three quarters of CVD deaths take place in low- and middle-income countries. The number of deaths caused by ischemic heart disease has increased the most, and also the number of deaths caused by Alzheimer's disease and diabetes has increased. Respiratory infections caused most deaths by a communicable disease with 11.2 million deaths in the world in 2021, out of which COVID-19 caused 8.7 million deaths (World Health Organization, 2024).

Also in Finland CVDs as a group cause the most deaths followed by cancers and dementias in general population as well as in older population of 65-year-olds and older. CVD mortality has decreased but it is still the underlying cause of death in about one third of all deaths in Finland. Coronary artery disease causes about half of CVD deaths with similar rates for both men and women. Dementia including Alzheimer's disease has risen to be the most common single cause of death in Finland causing one fifth of all deaths (Official Statistics Finland, 2024).

3 Aims

This thesis aimed to create indexes based on routine laboratory analytes and to investigate their associations with mortality and institutionalization, and to study the associations of cTnT and proBNP on all-cause and CV mortality in older population. In addition, we used our study population to create reference limits for cTnT and proBNP in older population.

The specific aims were:

1. To analyze whether a laboratory index based on 14 commonly used laboratory tests can be used to evaluate the risk of institutionalization and mortality among Finnish older people during 10- and 18-year follow-ups (Study I)
2. To create indexes to predict the risk for mortality and institutionalization with as few parameters as possible without compromising their predictive ability (Study II)
3. To define reference limits for cTnT and proBNP that would better reflect their concentrations in older people and could be applied in clinical use (Study III)
4. To study the associations of cTnT and proBNP with the incidence of AMIs in an older population with and without previous heart diseases, and their association with CV and all-cause mortality in older population in non-acute conditions (Studies III and IV)

4 Material and Methods

4.1 Study population

This study is part of the Lieto elderly study, which is a longitudinal epidemiological study carried out in the municipality of Lieto in south-western Finland (Löppönen et al., 2003). All persons born in or prior to the year 1933 (n=1596) were invited to participate in the baseline examination which was carried out between March 1998 and September 1999. Of those eligible, 63 died before they were examined, and 273 refused or did not respond, leaving 1260 (82%) participants, 533 men and 727 women. They were followed for institutionalization and mortality for 18 years for study I, and ten years for study II. For study IV, the participants were followed for ten years for CV and all-cause mortality.

Participants no longer living in Lieto at the end of 2016 (n=86) were excluded from the analyses predicting institutionalization, as it was not possible to ascertain whether they were institutionalized in their current municipality or whether they lived at home. Sixty-eight participants were already living in institutional care at the start of the study and were excluded from the institutionalization analyses. After these exclusions, there were 1106 participants in the institutionalization analyses.

For study I, participants with missing data of analytes needed for the laboratory index (n=107) were excluded leaving 1153 participants for the final study cohort predicting mortality. Data was missing for 87 of those that were left in the institutionalization analyses, leaving 1019 participants. For study II, participants with missing data of more than five percent of the parameters included in the indexes (n=88 for mortality and n=52 for institutionalization) were excluded leaving 1172 and 1054 participants for the analyses predicting mortality and institutionalization, respectively.

For the reference population in study III, all individuals with a kidney disease (International Statistical Classification of Diseases and Related Health Problems 10th Revision [ICD-10] codes N00–N29) at baseline (n=52) or with missing data (n=10) were excluded. Of those without kidney diseases, 435 already had a diagnosis of a heart condition (ICD-10 codes I20–I25, I30–I52 including ischemic heart diseases and other heart diseases) at baseline and were also excluded from the

reference population. This left us with 763 individuals who formed the reference population for cTnT and proBNP.

The 435 participants with a previous diagnosis of a heart disease at baseline were used to test the association of the newly created reference ranges with the incidence of AMIs in older population with a previous heart condition.

For study IV on all-cause and CV mortality, all individuals with a kidney disease at baseline (n=52) or with missing data (n=10) were excluded from the study population, leaving 1198 participants for mortality analyses.

4.2 Methods

4.2.1 Baseline examination

Data for the clinical parameters were gathered from a doctor's clinical examination including a comprehensive interview and a survey of patient records at baseline. Cross-sectional data collected between March 1998, and September 1999 were used as baseline information. All study participants were clinically carefully examined, including a comprehensive interview with history, lifestyle, and previous diagnoses, Rose questionnaire, numerous laboratory analyses and an electrocardiogram examination (Löppönen et al., 2003).

4.2.2 Laboratory measurements

Venous blood samples were obtained with minimal stasis between 8 and 10 am after overnight fast at Lieto Health Centre. All participants were given verbal and written instructions on preparing for the blood sample collection before the laboratory visit. Blood samples were collected, centrifuged and aliquots of serum were stored at -70°C. The analytes that were used for the index studies were analysed from fresh samples at the Central laboratory of Turku University hospital at the time of the baseline examination.

The analyses of high sensitivity cTnT and proBNP were performed from previously unthawed stored samples at the Central laboratory of Turku University Hospital during December 2020. The determination of cTnT and proBNP were performed on a Cobas® 8000 e801 analyser using electrochemiluminescence immunoassay (ECLIA) method (Roche Diagnostics, Mannheim, Germany; for cTnT the limit of detection (LoD) 3 ng/L, the limit of quantification (LoQ) (10% coefficient of variation) 13 ng/L, and for proBNP LoD 5 ng/L, LoQ (20% coefficient of variation) 50 ng/L). The mean coefficients of variation for two-level controls were 3.0% and 3.8% for cTnT, and 2.7% and 2.8% for proBNP.

4.2.3 Institutionalization

Institutionalization was defined as permanent entry into long-term care of which the data were gathered from the municipality's electronic patient record system and coded by month and year of entry. Eighty-six participants were excluded because they had moved to another municipality during the follow-up period, and their institutionalization could not be ascertained. Sixty-eight participants were already living in institutional care at baseline and excluded from the institutionalization analyses.

4.2.4 Mortality

Data from all participants who died by the end of 2016 for study I, and by the end of 2008 for studies II, III and IV were obtained from the Statistics of Finland Causes of Death -registry identified with unique personal identification numbers. In this study, the cause of death was defined as cardiovascular if the death was registered by ICD-10 codes I10–I15, I20–I25 or I30–I52.

4.2.5 The incidence of acute myocardial infarctions

The data on the participants' diagnoses for AMIs were collected from the municipality's electronic patient record system, the Finnish Hospital Discharge Register provided by the National Institute of Health and Welfare, and the Finnish Cause of Death Registry, from the Official Statistics Finland, from baseline examination up till the end of 2008, providing a follow-up period of 10 years. The diagnosis for AMI was based on ICD-10 codes I21 and I22.

4.2.6 The laboratory index

In study I we created a laboratory index (LI) comprising fourteen laboratory analytes. The laboratory analytes that constitute the LI and their reference ranges or cut-off values are shown in Table 1. The index is calculated as the proportion of individual's laboratory test results outside reference ranges in relation to the total number of analytes tested. For the index we chose some of the laboratory parameters that were defined at the beginning of the Lieto elderly study. They were selected so that they do not overlap significantly as risk indicators but reflect the health status of different organ systems and that they are routinely tested when examining older patients in Finland.

The LI was constructed by coding each analyte as either 0 or 1; 0 indicates that the value was within the normal range or cutoff and 1 that the value was above or below the normal range. The sum of these values was then divided by the total number of the analytes resulting in a score ranging from 0 to 1 for each individual.

To compare the adverse outcomes of individuals with different LI scores, we divided the participants in five categories (1. LI ≤0.08 [≤1 laboratory test result outside reference ranges], 2. LI 0.09–0.14 [2 laboratory test results outside reference ranges], 3. LI 0.15–0.21 [3 laboratory test results outside reference ranges], 4. LI 0.22–0.42 [4 to 5 laboratory test results outside reference ranges], and 5. LI ≥0.43 [≥6 laboratory test results outside reference ranges]).

Table 1. Reference ranges used for the analytes in the laboratory index for men and women

	Men	Women
Hemoglobin (g/L)	128-168	117-153
Albumin (g/L)	36.1-47.5	34.8-46.1
Calcium (mmol/L)	2.17-2.47	2.17-2.47
Urate (µmol/L)	180-420	130-340
TSH (mU/L)	0.4-4.5	0.4-4.5
Creatinine (µmol/L)	< 135	< 125
Ferritin (µg/L)	20-240	10-100
CRP (mg/L)	< 3	< 3
Sodium (mmol/l)	136-144	136-144
Potassium (mmol/L)	3.5-4.8	3.5-4.8
Glucose (mmol/L)	4.0-6.4	4.0-6.4
ALT (U/L)	< 50	< 35
ALP (U/L)	< 300	< 300
LDL cholesterol (mmol/L)	< 3.5	< 3.5

Abbreviations: TSH, thyroid stimulating hormone; CRP, C-reactive protein; ALT, alanine amino-transferase; ALP, alkaline phosphatase; LDL, low-density lipoprotein

4.2.7 The combined clinical and laboratory index

For study II, we combined the 36 clinical and 14 laboratory parameters that have been used in our earlier studies separately, to form an index with possibly a better predicting ability on mortality and institutionalization. The clinical parameters included 36 symptoms, signs, and disabilities similarly to other FIs (Mitnitski et al., 2001; Searle et al., 2008), and are shown in Table 2. The laboratory parameters were the same as in study I.

The combined index (LI+FI) was constructed similarly to the LI by coding each deficit or laboratory analyte as either 0 or 1 and dividing the sum of these values by the total number of the parameters resulting in a score ranging from 0 to 1. For this study, we used established cut-points that have been used in FIs (Song et al., 2010) (1. LI+FI ≤0.085, 2. LI+FI 0.085–0.2499, 3. LI+FI ≥0.25) and thus divided the participants in these three categories.

Table 2. The clinical parameters used in the combined indexes

Needs help with toileting [1 2]
Needs help with dressing and undressing [1 2]
Needs help with preparing meals [1 2]
Needs help with house work [1 2]
Needs help with heavy household chores [1 2]
Needs help with personal care [1 2]
Needs help with moving about inside house [1 2]
Arthritis or rheumatism
High blood pressure [1]
Chronic bronchitis or emphysema
Diabetes mellitus [1]
Heart disease[a] [1]
Cancer [1]
Stomach or intestinal ulcers
Suffers from the effect of stroke [1]
Urinary incontinence [2]
Stool incontinence [2]
Shortness of breath [1 2]
Angina pectoris [1]
Other medical problems[b] [1]
No regular physical exercise [1 2]
Vision problem [1 2]
Hearing problem [1 2]
Feeling hopeless [1]
Emotional problem [2]
Memory problem [1 2]
Bodily pain [2]
Speech problem [1]
Resting tremor [1]
Five or more medications [1 2]
Difficulties carrying or lifting light loads [1 2]
Mobility problem [1 2]
Limited kind of amount of activity [1 2]
Feeling tired all the time [1 2]
Weight loss [2]

[a]Known heart disease at baseline (ICD-10: I20-I25, I48, I49)
[b]Other disease at baseline (ICD-10: E03, E05, G20, G35, J44-J46, M15-M17, M47)
[1] Independently associated with 10-year-mortality in univariable analysis
[2] Independently associated with 10-year-institutionalization in univariable analysis

4.3 Statistical analyses

HRs and their 95% confidence intervals for institutionalization in studies I and II, all-cause mortality in studies I, II and IV, CV mortality in study IV and the incidence of AMIs in study III were calculated using Cox proportional hazard models. Proportional hazards assumption was tested using Martingale residuals. The follow-up periods were calculated from the baseline examination and measurements to the end of the follow-up period of 10 or 18 years or to the death of the individual. Death was used as a competitive factor in the Cox regression analyses for institutionalization and in the analyses for AMIs. For studies I and II, unadjusted and age- and gender-adjusted analyses were conducted. For study IV for the analyses of the associations of cTnT and proBNP with all-cause and CV mortality, the analyses were adjusted also for other statistically significant baseline characteristics.

P-values less than 0.05 were considered statistically significant. All statistical analyses were performed using SAS System for Windows, version 9.4 (SAS Institute Inc., Cary, NC, USA).

The formation of the reduced indexes in study II was started by selecting those clinical and laboratory parameters that were associated with institutionalization or mortality in the univariable Cox regression analysis. There were no significant correlations between different laboratory parameters but some of the clinical parameters correlated significantly and were left out from the reduced indexes. A backward stepwise Cox regression analysis (exclusion criteria, $p \geq 0.05$) was performed to identify the parameters which best predicted mortality and institutionalization and to reduce the number of parameters in the index (Collett, 2014). The reduced indexes were also calculated by including age (64–69, 70–74, 75–79, 80 or over) and gender to the indexes. Clinical and laboratory parameters were scored with 0 or 1 points, female gender was scored with 1 point for the institutionalization index and male gender with 1 point for the mortality index, and age was scored with 0 points for ages 64 to 69, 1 point for ages 70 to 74, 2 points for ages 75 to 79 and 3 points for the age of 80 or over, based on the parameter estimates of the stepwise Cox regression model and statistical testing in the effect of different weights on the index. This resulted in a range of 0 to 7 for the combined index to predict institutionalization and a range of 0 to 13 to predict mortality. Receiver-operating characteristic curves were used to define the cut-off points for the reduced indexes to predict institutionalization and mortality (Gonen, 2007). The optimal cut-off points were chosen using Youden index (Youden, 1950). Sensitivity, specificity, positive predictive value and negative predictive value for cut-off points were calculated. Kaplan-Meier survival curves for institutionalization and mortality during the 10-year follow-up were implemented to compare participants below and above the cut-off points (Collett, 2014).

For the creation of reference limits for cTnT and proBNP, Mann-Whitney U-test was used to compare the concentrations between age groups and genders. The distributions of cTnT and proBNP values were skewed, and therefore log-transformed for reference limit calculations. Normal distribution method was used to calculate 97.5% reference limits (mean+1.96× standard deviation [SD]) with their corresponding 95% confidence intervals after exclusion of outliers according to the 3 SD criterion. For cTnT we defined also the 99% reference limit (mean+2.33×SD) that is recommended for the diagnosis of AMI (Thygesen et al., 2018). After the reference limits were calculated, the values were transformed back to the original units.

In study IV, the mortality of the highest and lowest quartiles of the analytes were compared to study the associations of cTnT and proBNP with all-cause and CV mortality in each group.

4.4 Ethics

The Lieto Elderly Study was conducted according to the guidelines of the Declaration of Helsinki. The Ethics Committee of the Hospital District of Southwest Finland approved the study protocol (Diary number 112/1802/2015). Participants provided written informed consent for the study.

5 Results

5.1 Characteristics of the participants

The mean age of the participants (n=1259) at baseline (1998–1999) was 73.5 years (SD 6.8, range 64–100), 532 were men (42 %), and 727 women (58 %). Most study participants (88%) had basic or less than basic level of education defined as six years of elementary school, and only 12% more than basic education. Most participants (72%) had a Mini Mental State Examination score of more than 25 points. Most participants were living with someone, and 30% were living alone.

Some participants were excluded from each study resulting in slightly different numbers of participants (Figure 4). Baseline characteristics for the participants for study I are shown in Table 3.

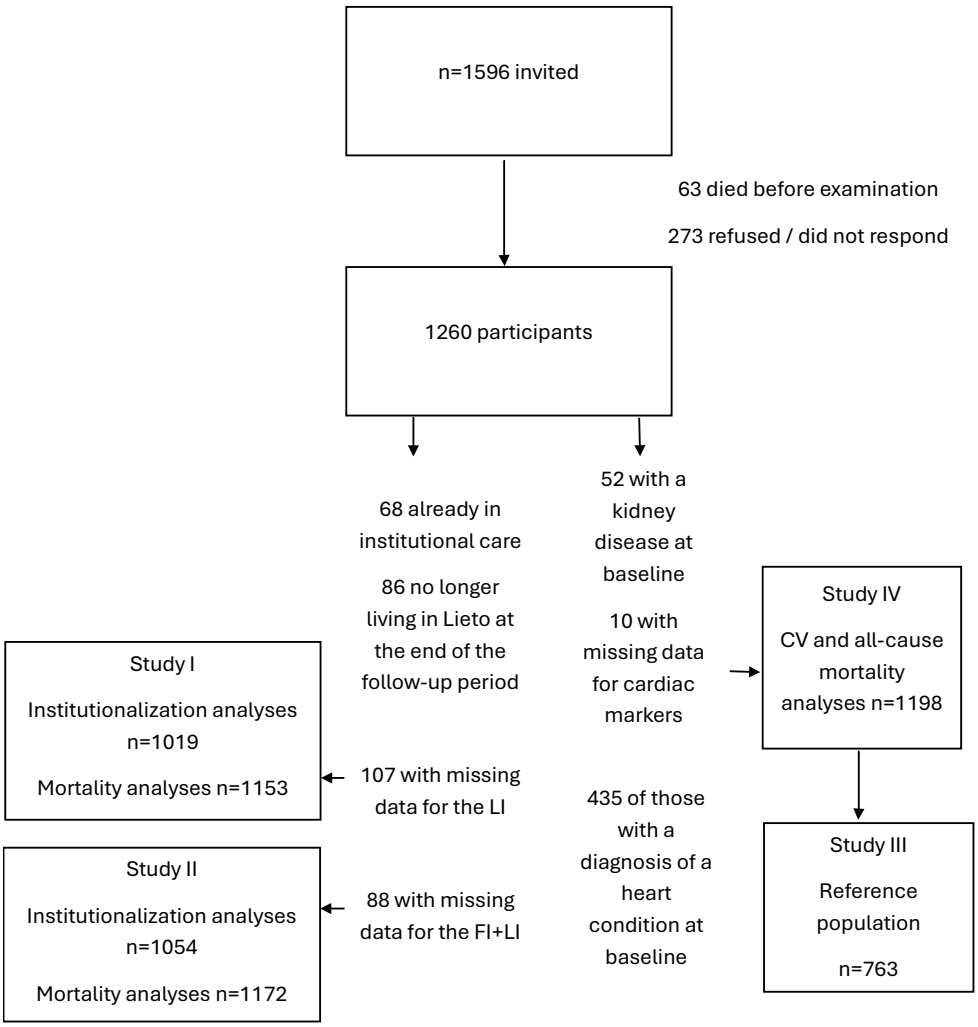


Figure 4. Flow chart of the study participants. Abbreviations: LI, laboratory index; FI+LI, combined clinical and laboratory index; CV, cardiovascular.

Table 3. Baseline characteristics of study participants for mortality analyses in study I (n=1153)

	n (%)
Age, mean (SD), range	73.6 (6.8), 64–100
Age	
64–74	720 (62)
75–84	334 (29)
≥85	99 (9)
Women	663 (58)
Living alone	344 (30)
Education	
Basic[a] or less than basic	1050 (91)
More than basic	103 (9)
Mini Mental State Examination ≤26	323 (28)
Body mass index, kg/m^2	
<20	68 (6)
20–24.9	317 (28)
25–29.9	498 (43)
30–34.9	206 (18)
≥35	61 (5)
Number of prescribed medicines	
<5	855 (74)
5–7	207 (18)
8–9	66 (6)
≥10	25 (2)

[a]Six years of elementary school

5.2 Index studies

5.2.1 The laboratory index

5.2.1.1 Prediction of mortality (Study I)

Altogether, 422 (37%) and 806 (70%) subjects deceased during the 10- and 18-year follow-ups, respectively.

Higher LI predicted increased mortality. Index scores of 0.09 or over and 0.15 or over, predicted increased mortality during the 10- and 18-year follow-ups, respectively (Tables 4 and 5). These associations persisted after adjustments for age and gender. Figure 5 shows Kaplan-Meier survival curves by the categories of LI.

Table 4. Hazard ratios (HR) and their 95% confidence intervals (CI) (in parentheses) of the laboratory index (LI) for mortality during the 10-year follow-up

	Total n	Deceased n (%)	Unadjusted HR (95% CI)	P-value	Adjusted[a] HR (95% CI)	P-value
LI						
≤0.08[b]	383	92 (24)	1			
0.09–0.14[c]	326	119 (36)	1.61 (1.23–2.12)	<0.001	1.69 (1.28–2.22)	<0.001
0.15–0.21[d]	211	87 (41)	1.96 (1.46–2.63)	<0.001	1.84 (1.37–2.48)	<0.001
0.22–0.42[e]	190	93 (49)	2.46 (1.84–3.28)	<0.001	2.20 (1.64–2.94)	<0.001
≥0.43[f]	43	31 (72)	5.56 (3.71–8.40)	<0.001	3.75 (2.46–5.72)	<0.001
Total	1153	422 (37)				

[a]Values are adjusted for age and gender

The number of laboratory values outside reference ranges by categories of LI:
[b]0–0.08 ≤1
[c]0.09–0.14 =2
[d]0.15–0.21 =3
[e]0.22–0.42 =4–5
[f]0.43– ≥6

Table 5. Hazard ratios (HR) and their 95% confidence intervals (CI) (in parentheses) of the laboratory index (LI) for mortality during the 18-year follow-up

	Total n	Deceased n (%)	Unadjusted HR (95% CI)	P-value	Adjusted[a] HR (95% CI)	P-value
LI						
≤0.08[b]	383	242 (63)	1			
0.09–0.14[c]	326	213 (65)	1.14 (0.95–1.37)	0.169	1.17 (0.98–1.41)	0.091
0.15–0.21[d]	211	160 (76)	1.51 (1.23–1.84)	<0.001	1.47 (1.20–1.80)	<0.001
0.22–0.42[e]	190	152 (80)	1.80 (1.47–2.20)	<0.001	1.72 (1.40–2.12)	<0.001
≥0.43[f]	43	39 (81)	3.41 (2.43–4.79)	<0.001	2.93 (2.07–4.16)	<0.001
Total	1153	806 (70)				

[a]Values are adjusted for age and gender

The number of laboratory values outside reference ranges by categories of LI:
[b]0–0.08 ≤1
[c]0.09–0.14 =2
[d]0.15–0.21 =3
[e]0.22–0.42 =4–5
[f]0.43– ≥6

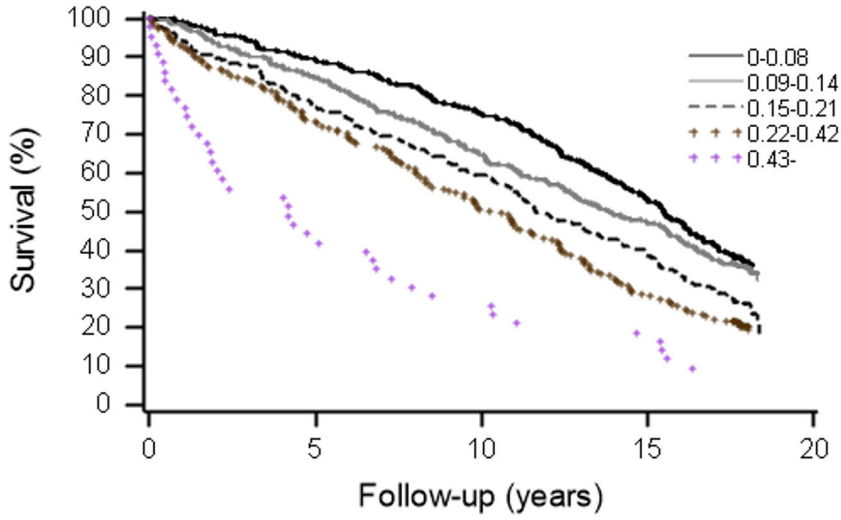


Figure 5. Survival curves by the laboratory index (LI) comprising 14 commonly used laboratory tests during the 18-year follow-up. Reprinted from Study I (Heikkilä et al., 2021).

The number of laboratory values outside reference ranges by categories of LI:

0–0.08	≤1
0.09–0.14	=2
0.15–0.21	=3
0.22–0.42	=4–5
0.43–	≥6

5.2.1.2 Prediction of institutionalization (Study I)

Altogether, 151 (15%) and 305 (30%) subjects were institutionalized during the 10- and 18-year follow-ups, respectively. The LI did not significantly predict institutionalization during either of the follow-ups in unadjusted or age- and gender-adjusted models (data not shown).

5.2.2 The combined index

5.2.2.1 Prediction of institutionalization (Study II)

Altogether 149 (14%) subjects were institutionalized during the 10-year follow-up.

Higher index score of the 50-parameter combined index was associated with an increased risk of institutionalization in the 10-year follow-up. Both groups with LI+FI 0.085–0.2499 and LI+FI 0.25 or over had statistically significantly higher risk of institutionalization compared to the group with LI+FI less than 0.085 with HRs 2.42 and 6.64, respectively. These associations persisted after adjustments for age and gender.

5.2.2.2 Prediction of mortality (Study II)

Altogether 413 (35%) subjects deceased during the 10-year follow-up.

Higher index score of the 50-parameter combined index was associated with an increased risk of death in the 10-year follow-up. Both groups with LI+FI 0.085–0.2499 and LI+FI 0.25 or over had a statistically significantly higher risk of death compared to the group with LI+FI less than 0.085, with HRs 2.23 and 9.39, respectively. These associations remained statistically significant when adjusted for age and gender.

5.2.3 The reduced indexes

5.2.3.1 Prediction of institutionalization (Study II)

Twenty-two clinical parameters from the large, combined index were independently associated with 10-year-institutionalization (Table 2). Hemoglobin was the only laboratory analyte that was statistically significantly associated with institutionalization. After a backward variable selection in the Cox regression model, the parameters that were left for the reduced index to predict institutionalization were need for help with preparing meals, need for help with heavy household chores and need for help with moving about inside house. Female gender and increasing age were significant predicting factors for institutionalization and adding these factors to the index improved its predictive ability (Table 6). Each factor was coded either 0 or 1; 0 indicates that the person did not need help with the task and 1 that the person needed help. One point was given for female gender and 0 to 3 points for increasing age resulting in a range of 0 to 7 for the index score. The parameters and their scoring can be seen in Table 7. The best cut-off limit for the increased risk of institutionalization was found to be ≥4 points.

The reduced index with the chosen optimal cut-off limit showed a much greater sensitivity in comparison to the 50-parameter combined index with the cut-off limit 0.25 habitually used for FIs. Using this cut-off limit, the specificity of the larger index was higher than the specificity of the reduced index. The largest area under the curve (0.78) was found for the reduced index that included age and gender with a sensitivity of 74.7% and a specificity of 69.4% for the institutionalization index (Table 6).

The higher the index score, the higher percentage of our study population were institutionalized during the 10-year-follow-up period. This can be seen in figure 6a. Figure 7a shows Kaplan-Meier survival curve by the cut-off limit of 4 points.

Table 6. AUC-values, cut-off limits and their sensitivities, specificities and positive and negative predictive values for the 50-parameter combined index and for the reduced indexes in predicting 10-year institutionalization and mortality

	AUC (95 % CI)	Cut-off limit (scale)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Institutionalization						
50-parameter combined index	0.71 (0.66–0.75)	≥0.25* (0–1)	38.3	84.9	29.4	89.3
Reduced index without age and gender	0.74 (0.70–0.78)	≥2** (0–3)	71.0	71.8	30.2	93.5
Reduced index with age and gender	0.78 (0.75–0.82)	≥4** (0–7)	74.7	69.4	29.6	94.1
Mortality						
50-parameter combined index	0.77 (0.74–0.80)	≥0.25* (0–1)	42.5	92.0	74.2	74.7
Reduced index without age and gender	0.79 (0.77–0.82)	≥5** (0–9)	61.8	84.2	69.5	79.2
Reduced index with age and gender	0.83 (0.80–0.85)	≥8** (0–13)	77.0	75.8	64.9	85.1

*Habitual cut-off limit for a frailty index

**Best cut-off limit defined by Youden index

Abbreviations: AUC, area under the curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value

5.2.3.2 Prediction of mortality (Study II)

Twenty-seven clinical parameters and eleven laboratory parameters from the large, combined index were independently associated with 10-year-mortality (Table 2). The laboratory analytes associated with mortality were hemoglobin, albumin, calcium, urate, TSH, alanine aminotransferase, creatinine, ferritin, CRP, sodium, potassium, glucose and alkaline phosphatase. The reduced index for mortality included three laboratory analytes and six clinical parameters. The parameters were elevated or decreased blood hemoglobin value, elevated plasma CRP level, and elevated or decreased plasma sodium level, the need for help with preparing meals, the need for help with heavy household chores, difficulties carrying or lifting light loads, limited kind of amount of activity, diabetes mellitus and heart disease. One point was given for each of these deficits or a laboratory value outside the reference ranges. Increasing age and male gender were significant predicting factors for mortality so, similarly to the index predicting institutionalization, 0 to 3 points was given for age and 1 point for male gender. This resulted in a score ranging from 0 to 13 with the best cut-off limit being ≥8 points for the prediction of a person being at an increased risk of death. The parameters and their scoring can be seen in Table 7.

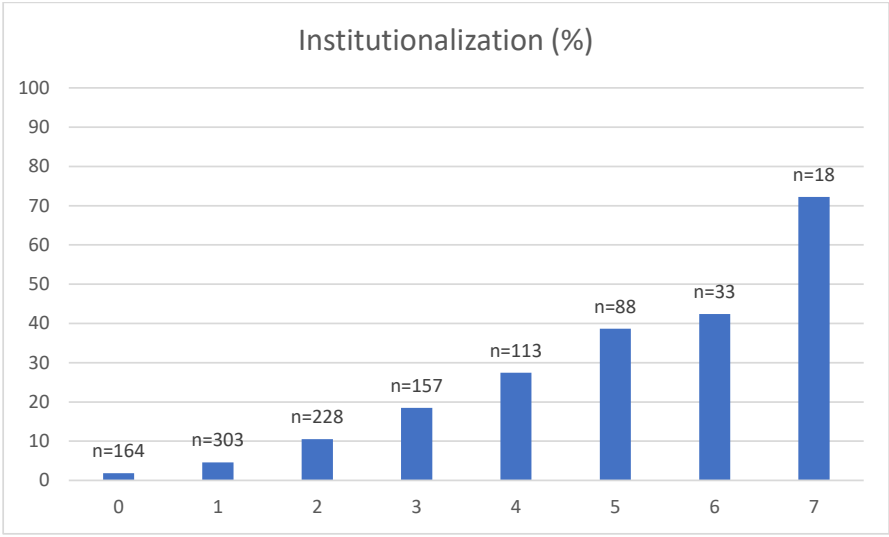
Increasing index score increased deaths in the study population during the 10-year-follow-up period as seen in figure 6b. Figure 7b shows the Kaplan-Meier survival curve by the cut-off limit of 8 points.

When comparing the reduced and large combined indexes, sensitivity was higher for the reduced index using the chosen cut-off limit, but specificity higher for the larger index. The reduced index that included age and gender showed the largest area under the curve (0.83) with a sensitivity of 77.0% and a specificity of 75.8% for the mortality index (Table 6).

Table 7. The parameters and their scoring for the reduced indexes

	Index points
Institutionalization	
Needs help with preparing meals	1
Needs help with heavy household chores	1
Needs help with moving about inside house	1
Female gender	1
Age 70 to 74	1
Age 75 to 79	2
Age 80 or more	3
Total index score	**0–7**
Mortality	
Elevated or decreased blood hemoglobin value	1
Elevated plasma c-reactive protein level	1
Elevated or decreased plasma sodium level	1
Needs help with preparing meals	1
Needs help with heavy household chores	1
Difficulties carrying or lifting light loads	1
Limited kind of amount of activity	1
Diabetes mellitus	1
Heart disease	1
Male gender	1
Age 70 to 74	1
Age 75 to 79	2
Age 80 or more	3
Total index score	**0–13**

A



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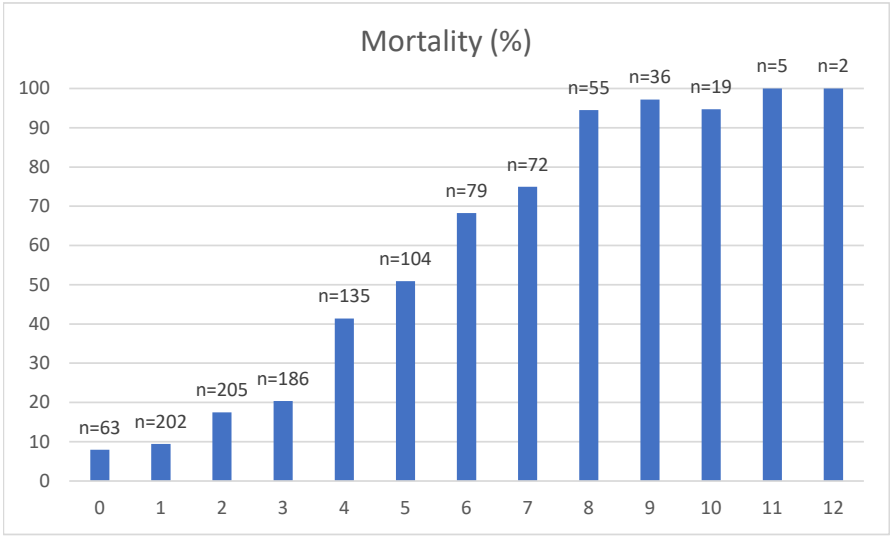

Figure 6. Institutionalization (A) and mortality (B) rates by each index score during the 10-year follow-up. Reprinted from Study II (Heikkilä et al., 2023).

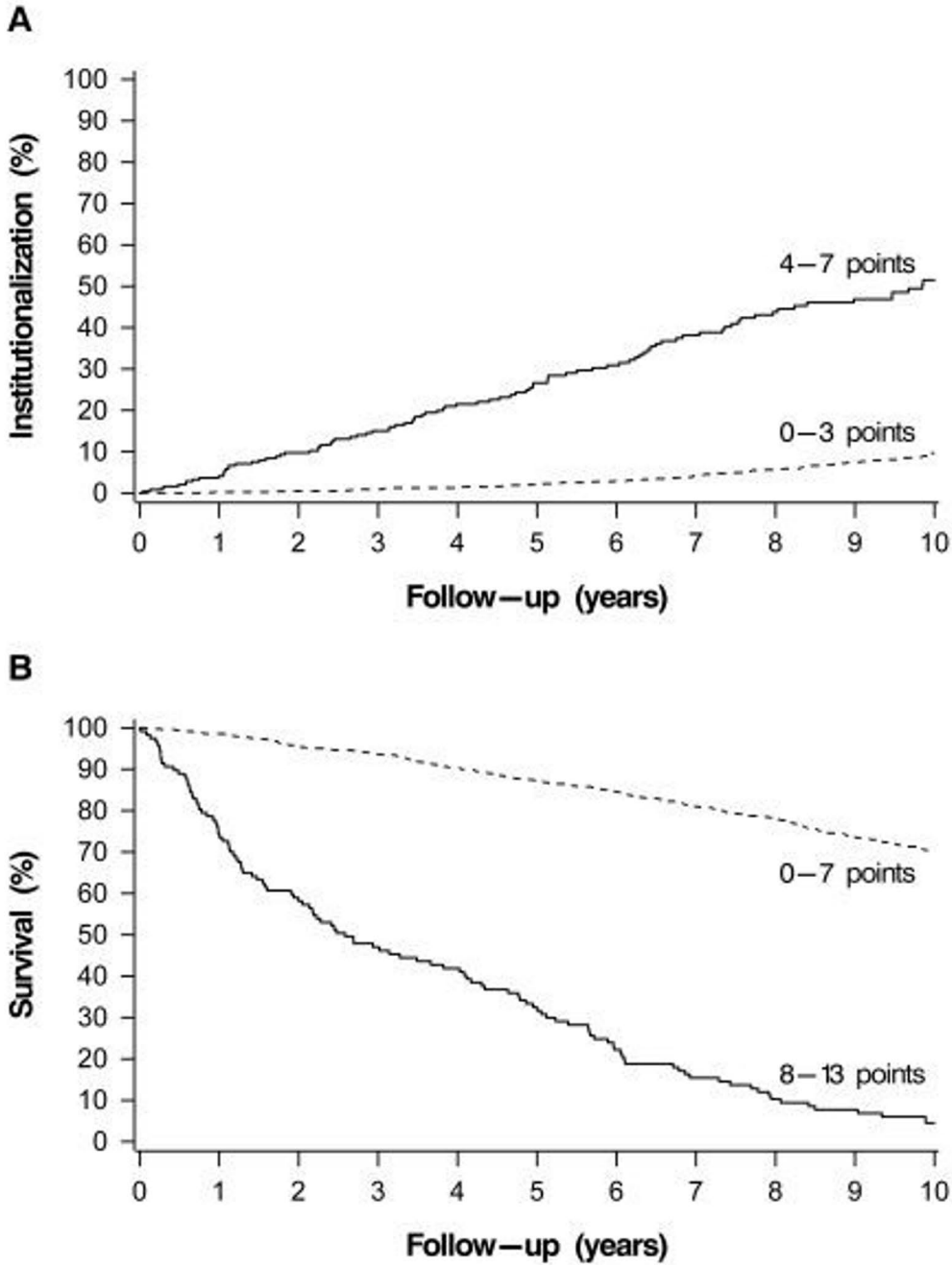

Figure 7. Rates of institutionalization by the reduced index with the cut-off score ≥4 (A) and mortality by the reduced index with the cut-off score ≥8 (B) during the 10-year follow-up. Age and gender are included in both reduced indexes. Reprinted from Study II (Heikkilä et al., 2023).

5.3 Cardiac marker studies

5.3.1 Baseline characteristics of the reference population (Study III)

The reference population was formed by 763 individuals, 308 men and 455 women aged over 64 years. The mean age of the men was 72.1 years (SD 6.2), and the mean age of the women 72.8 years (SD 6.4). 435 participants with a previous heart disease were excluded from the reference population, 193 men, whose mean age was 73.5 years (SD 6.4) and 242 women, whose mean age was 76.3 years (SD 7.5).

The median concentrations of cTnT among the reference population were 10.9 ng/L (interquartile range [IQR] 8.2–15.2) for men, and 9.2 ng/L (IQR 6.5–12.2) for women. The median concentrations of cTnT among the population with a previous heart disease were 14.1 ng/L (IQR 10.1–22.1), and 10.7 ng/L (IQR 7.8–19.0), respectively.

The median concentrations of proBNP among the reference population were 81 ng/L (IQR 47–153) for men and 123 ng/L (IQR 75–210) for women. The median concentrations of proBNP among the population with a previous heart disease were 201 ng/L (IQR 94–617), and 259 ng/L (IQR 116–635), respectively.

The median concentrations of cTnT and proBNP in different age groups among the reference population are shown in Table 8. The relation of cTnT and proBNP concentrations with age in the reference population can be seen in Figure 8.

Table 8. Median concentrations and interquartile ranges (IQR) of cardiac troponin T (cTnT) and N-terminal natriuretic b-type propeptide (proBNP) in different age groups among the reference population

	n	Median concentration of cTnT (ng/L)	IQR	Median concentration of proBNP (ng/L)	IQR
Men					
64 to 69 years	138	9.0	6.9–12.1	64	34–118
70 to 74 years	85	10.7	8.3–13.4	75	47–121
74 to 79 years	49	14.6	10.7–19.4	115	79–186
Over 80 years	38	16.7	13.3–31.2	131	66–239
Women					
64 to 69 years	176	6.9	5.3–9.5	91	59–158
70 to 74 years	130	8.8	6.8–11.2	113	76–170
74 to 79 years	77	10.4	7.7–13.9	133	103–214
Over 80 years	76	15.3	10.9–21.7	219	125–355

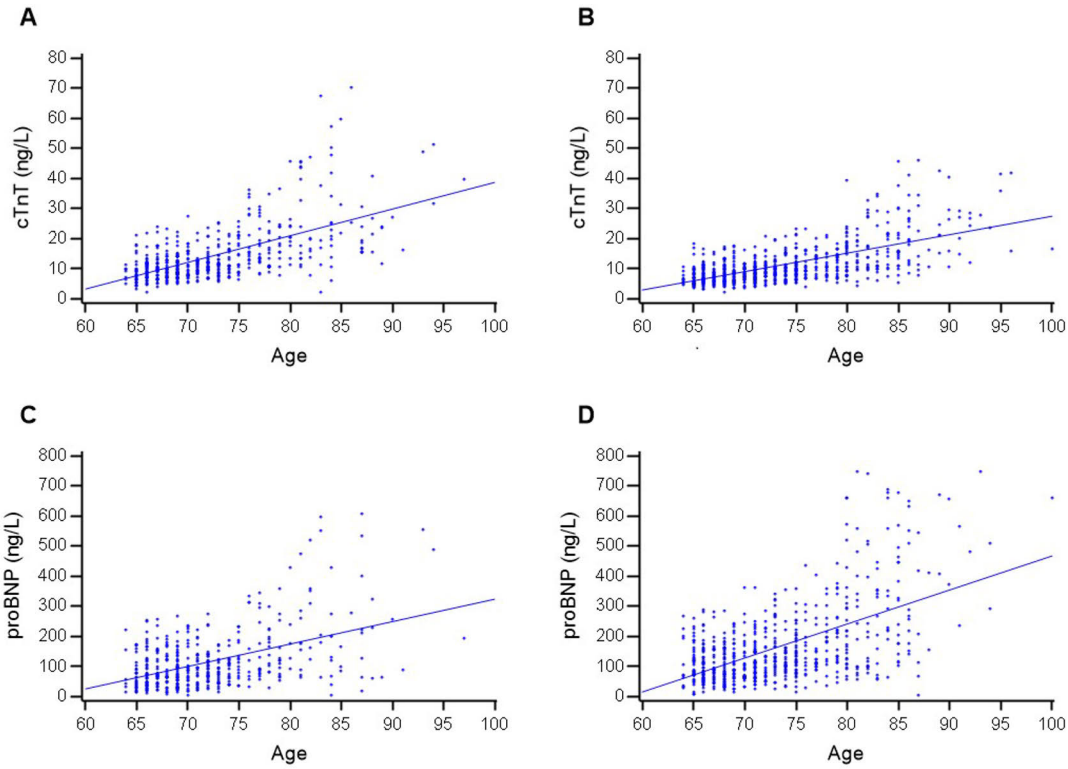

Figure 8. The relation of cardiac troponin T (cTnT) in men (A) and women (B), and N-terminal natriuretic b-type propeptide (proBNP) in men (C) and women (D) with age in the reference population. Reprinted from Study III (Heikkilä et al., 2024).

5.3.2 Reference limits for troponin T and N-terminal b-type natriuretic propeptide (Study III)

The reference limits were defined separately for both genders in four age groups because of statistically significant age group and gender differences in cTnT and proBNP values.

For cTnT, we calculated a 99% reference limit of 25 ng/L for men aged 64 to 69 years, 28 ng/l for men aged 70 to 74 years, 38 for men aged 75 to 79 years, and 71 for men aged 80 years and older, and 18 ng/L, 22 ng/l, 26 ng/l, and 52 ng/L for women, respectively. The 97.5% reference limits for proBNP were 272 ng/L, 287 ng/l, 373 ng/l and 686 ng/L for men, and 341 ng/L, 377 ng/l, 471 ng/l, and 794 ng/L for women, respectively (Table 9).

Table 9. Reference limits and their 95% confidence intervals (CI) for cardiac troponin T (cTnT) and N-terminal natriuretic b-type propeptide (proBNP)

	cTnT					proBNP		
	n	97.5% reference limit	95% CI for reference limit	99% reference limit	95% CI for reference limit	n	97.5% reference limit	95% CI for reference limit
Men								
64 to 69 years	136	22	19–24	25	22–29	133	272	217–342
70 to 74 years	82	24	21–28	28	24–32	78	287	217–380
74 to 79 years	48	32	27–39	38	31–46	44	373	273–509
80 years and older	37	58	42–79	71	52–97	31	686	417–1130
Women								
64 to 69 years	174	16	14–18	18	17–20	168	341	285–409
70 to 74 years	124	19	17–21	22	19–24	122	377	312–455
74 to 79 years	75	23	19–27	26	23–31	73	471	366–607
80 years and older	74	43	35–53	52	42–63	67	794	603–1045

5.3.3 The associations of troponin T and N-terminal b-type natriuretic propeptide with the ten-year incidence of acute myocardial infarctions (Study III)

There were 109 new AMIs in the whole study population during the 10-year follow-up period, and 53 of those in the population who already had a previous diagnosis of a heart disease.

Out of the 401 participants with a heart disease and a normal cTnT level at baseline 46 (11%), and out of the 34 participants with a heart disease and an elevated cTnT seven (21%) had an AMI during the follow-up period.

There were 299 participants with a heart disease who had a normal proBNP level at baseline and 29 (10%) of those had an AMI, whereas there were 136 participants with a heart disease and an elevated proBNP level and 24 (18%) of those had an AMI during the follow-up period.

According to the Cox regression analyses, there were no statistically significant associations of elevated cTnT above the 99% reference limit with the incidence of AMIs during the 10-year follow-up period among participants with and without a previous heart disease, HRs 2.0 (0.88–4.56) and 2.20 (0.80–6.06), respectively. Elevated proBNP was statistically significantly associated with the incidence of AMIs both among participants with and without a previous heart disease, HRs 1.95 (1.13–3.35) and 2.54 (1.25–5.17), respectively.

5.3.4 The associations of troponin T and N-terminal b-type natriuretic propeptide with cardiac and all-cause mortality (Study IV)

Of the 1198 participants in this study, 676 had a CVD, 430 of those had hypertension, and 254 had coronary artery disease. 174 participants had diabetes.

The median concentration of cTnT was 11.7 ng/L for men (IQR 8.7–17.9) and 9.7 ng/L for women (IQR 6.9–14.6). The median concentration of proBNP was 117 ng/L for men (IQR 63–240) and 148 ng/L for women (IQR 84–300).

A total of 467 (37 %) subjects deceased during the 10-year follow-up period, and 149 of those of a CVD.

There were statistically significant age group and gender differences in both cTnT and proBNP concentrations. We divided the population into 64–74-year-olds, and over 75-year-olds because cTnT (median 8.9 ng/L vs 15.5 ng/L, $p<.001$) and proBNP (median 104 ng/L vs 230 ng/L, $p<.001$) increased significantly with age. Women had lower concentrations of cTnT ($p<.001$) and higher concentrations of proBNP ($p<.001$), and genders were analysed separately.

Both elevated cTnT and proBNP concentrations were statistically significantly associated with CV and all-cause mortality during the 10-year follow-up period in

each group without adjustments. cTnT was statistically significantly associated with CV and all-cause mortality in over 75-year-old men and women when adjusted for the statistically significant baseline factors, but in the younger age group statistical significance was not reached. ProBNP was significantly associated with CV mortality in both age groups in men and women also when adjusted for the baseline factors, and in over 75-year-old men and 64–74-year-old women for all-cause mortality.

6 Discussion

This thesis provides new indexes for clinical use for the prediction of institutionalization and mortality in a population aged 65 years and older. Other main results include the confirmation of the predictive value of cTnT and proBNP for CV events and CV and all-cause mortality in older Finnish population. We defined reference limits on our representative older study population and confirmed the previous finding that the conventional reference limits are not valid for older population.

The indexes created in this thesis may aid clinicians in identifying those at high risk of adverse health outcomes. To be of value, indexes must be easy enough to apply in use, which is why we tried to reduce the number of parameters in the indexes. Earlier, there have been FIs mostly comprising clinical deficits that are used for the prediction of adverse outcomes including institutionalization and mortality. Different previously formed clinical FIs have been shown to apply also in our study population (Salminen et al., 2019; Viljanen et al., 2021).

Indexes to predict frailty and adverse outcomes have also been based on laboratory parameters instead of clinical findings (Howlett et al., 2014; Blodgett et al., 2019). Some studies have found strong and some weak correlations between clinical FIs and laboratory-based indexes (Blodgett et al., 2016; Howlett et al., 2014; Ritt et al., 2017; Rockwood et al., 2015; Yang et al., 2018). Whereas clinical findings may be easy to obtain for an experienced clinician based on a clinical examination and a thorough interview, limitations in time and differences in both doctor's and patient's subjective assessment may complicate this evaluation. A distinct feature of a laboratory-based index compared with a clinical FI is that it may offer an opportunity to find deficits at cellular, molecular, or organ level prior to their clinical manifestations (Blodgett et al., 2017). Clinical and laboratory-based indexes are partly different entities, and do not always define the individual's risk similarly, although both can be used to predict mortality. On the other hand, also different clinical FIs define partly different people as frail (Salminen et al., 2019; Viljanen et al., 2021).

Studies have already proven the predictive ability of laboratory-based FIs, but the number of laboratory parameters in most FIs has been overly large to apply them

in use, for example, on a routine heath care visit of an older person. Especially considering the increasing number of older people, more simple and less time-consuming tools are needed, such as the fourteen-parameter LI that was created as part of this thesis study. The laboratory parameters used in the LI, as in most other formerly studied laboratory-based FIs, are measured from venous blood samples. Taking a venous blood sample can be considered an invasive procedure but with minimal risks of complications. Blood samples are commonly drawn prior or after a doctor's appointment so defining the analytes needed for the index would rarely require an additional laboratory visit. Also, the point of our index was to choose mostly analytes that are commonly examined as part of a health evaluation. The index score could be calculated automatically by laboratory information systems.

cTnT and proBNP are both proteins secreted or released by the myocardium (de Lemos et al., 2010; Martinez-Rumayor et al., 2008), and they can be used as biomarkers. Their elevated concentrations indicate an increased risk of CV mortality, but their predictive value can also be seen in their associations with total mortality in our study, and in earlier studies (de Lemos et al., 2010; Devereaux et al., 2012; Latini et al., 2007; Wang et al., 2004; Wang et al., 2019; Wu et al., 2018; Xu et al., 2013). Their concentrations increase with age, and separate but varying reference limits are in use for older people for proBNP, but not for cTnT. We defined new reference limits for both analytes in our study population. There was a significant rise in both analytes with age. Nevertheless, there were associations of increased concentrations of both markers measured in a non-acute situation and the incidence of future AMIs and with all-cause and CV mortality.

6.1 Study population

The data came from a community-based representative sample of Finnish older population, with a high participation rate (82%), and a long follow-up period. The study population consisted of a broad sample of the aged population living in the mid-sized semi-industrialized municipality of Lieto. At the time of the baseline examination, the percentage of the population aged over 65 years was 12 in Lieto, and 15 in the whole country. From the beginning of the study, the age structure in Finland has changed significantly with currently 24 percent of the population aged 65 years or over. The estimation for 2050 is 26 percent, and for 2070 31 percent (Official Statistics Finland, 2025). The gender distribution of the participants is comparable to the distribution of this age group in the whole country (Official Statistics Finland, 2025). Comparable age and gender structure at the time of the baseline examinations enables generalizability of the results to most Finnish municipalities. Nevertheless, Finland is a vast country with differences in population in different parts of the country such as the prevalence of CVDs in western and

eastern parts of the country (Finnish Institute for Health and Welfare, 2022). The reasons for these differences are unclear but likely due to both genetic differences and lifestyle factors such as the prevalence of cigarette smoking (Nuotio et al., 2020). These factors may lead to differences on how the created indexes and biomarkers predict outcomes in a certain population. Also, apart from the change of age structure, many other factors such as life habits and the prevalence of diseases may have changed from the time when this study was started. Testing the results in another population would be needed to ensure generalizability of the results to a specific population.

6.2 Findings

6.2.1 Laboratory index (Study I)

The results from study I suggest that an index based on fourteen routine laboratory analytes can be used to predict mortality in an older population. The LI was significantly associated with mortality but not with institutionalization during the 10- and 18-year follow-ups. The association of the LI with mortality remained after adjustments for age and gender.

Fourteen analytes is a small number of parameters compared to prior studies on laboratory-based FIs (Blodgett et al., 2017; Howlett et al., 2014; Ritt et al., 2017; Rockwood et al., 2015). In a systematic review and meta-analysis conducted in 2023 containing 38 studies on laboratory-based FIs, the number of the parameters ranged from the 14 parameters in our study to 77 parameters, with the average of 30 parameters. 93 percent of the included parameters were laboratory parameters. They found no difference in HRs between indexes including 20 to 25 parameters to those including 26 to 77 parameters, which supports the idea that less parameters may be enough if they reflect the health status of a variety of physiological systems (Sapp et al., 2023). In another review also conducted in 2023, 51 percent of the laboratory-based FIs included some non-laboratory parameters, most often pulse or blood pressure (Hakeem et al., 2023). In studies with a larger number of analytes, some analytes reflected the health status of the same or partly same organ system such as hemoglobin, red blood cells, mean corpuscular volume and hematocrit (hematopoiesis), or alanine aminotransferase, aspartate alanine transferase and gamma-glutamyl transferase (the liver) (Howlett et al., 2014; Ritt et al., 2017). In selecting the analytes that construct the LI in our study, care was taken that the information obtained from the analytes did not overlap significantly but captured information with respect to health status of different organ systems. Based on our study, it seems that fourteen analytes is

enough to achieve predictive value for mortality when the analytes are selected appropriately.

6.2.1.1 Associations of the laboratory parameters with mortality

Studies have found associations with mortality for all the fourteen analytes individually. Some of them have been more thoroughly studied than others, and some of them have strong evidence on their association with mortality. Especially anemia and inflammation are known to be risk factors for increased mortality, and thus a decreased hemoglobin level and an elevated CRP level have been found to be strongly associated with increased mortality. Anemia increases mortality from all causes in the older population, and the lowest mortality has been found at normal hemoglobin levels (Culleton et al., 2006; Shavelle et al., 2012). Anemia is also associated with reductions in functional capacity and quality of life. Anemia becomes progressively more common with age and is prevalent in both men and women over the age of 65 years. Common causes for anemia in older people are nutritional deficiencies and chronic diseases. Anemia is related to many diseases, but it seems to be related to ageing as well as it is estimated that one third of anemia in older patients is unexplained (Guralnik et al., 2022). Anemia related to ageing with no apparent underlying cause is likely multifactorial, with variable contributions from renal dysfunction, endocrine deficiency causing weaker response to erythropoietin, chronic inflammation, androgen deficiency and possibly beginning myelodysplasia (Guralnik et al., 2022).

Elevated levels of CRP have been shown to predict an increased risk of all-cause and CV mortality in the general population (Harris et al., 1999; Li et al., 2017). CRP levels are correlated with various CV risk factors, such as age, smoking status, hypertension, body mass index, frequency of exercise, and multiple lipid and non-lipid plasma-based indicators (Rohde et al., 1999). Ageing presents with systemic low grade chronic inflammation, and concentrations of many circulating inflammatory mediators rise with age (De Maeyer & Chambers, 2021; Harris et al., 1999). Chronic inflammation causes dysfunction of the immune system and strongly predicts morbidity and mortality. Increasing age is associated with increased incidence of infections and cancer, and decreased vaccine efficacy. This increased morbidity observed with age is believed to be due in part to a decline in adaptive immunity, termed immunosenescence (De Maeyer & Chambers, 2021). Inflammation is also a strong predictor for frailty, and the frailest have the highest levels of circulating CRP as well as other inflammatory mediators (Giovannini et al., 2011).

In addition to hemoglobin and CRP, deviating levels of each of the other analytes of the LI have associations with mortality. Creatinine is commonly used to estimate

glomerular filtration rate of the kidney that is associated with the risk of all-cause mortality (Willey et al., 2020). Kidney function slowly declines with age. The decline gradually impairs glomerular filtration and kidney's regulatory range of function that affects matching sodium and potassium excretion to dietary intake. Even when the kidney function declines, it is sufficiently preserved in healthy older people under normal conditions, but the homeostasis is challenged in extreme conditions or diseases (Gekle, 2017).

Studies have found associations with sodium levels and mortality in general population (Corona et al., 2013; Mohan et al., 2013), hospitalized patients (Waikar et al., 2009), and in patients with a chronic kidney disease (Kovesdy et al., 2012). Even a moderate serum sodium decrease was found to be associated with an increased risk of mortality in commonly observed clinical conditions. Hyponatremia develops in many conditions and is the most common electrolyte disorder in hospitalized patients. It is more common among aged patients, and with patients with hypertension, diabetes, coronary artery disease, stroke, chronic obstructive pulmonary disease, cancer, and psychiatric disorders, but remains associated with the risk of mortality when adjusted for age and comorbidities. A chronic hypotonic state beyond that of the underlying illness seems to affect the mortality risk (Corona et al., 2013).

Also hypo- and hyperkalemia are important electrolyte abnormalities that can both cause cardiac arrhythmias, and especially in patients with CV or renal disease. Low or high potassium levels are associated with increased mortality, but the risk is significantly greater in patients with comorbid conditions (Collins et al., 2017). Especially hyperkalemia, but also hypokalemia has been found to be associated with increased mortality especially in patients with hypertension (Krogager et al., 2017), chronic kidney disease, diabetes mellitus, or heart failure, and in older population (Collins et al., 2017). Possibly high and low potassium levels even within reference ranges may increase the risk for mortality, but the exact potassium levels associated with increased risk remain controversial (Collins et al., 2017; Krogager et al., 2017).

Increased or decreased concentrations of urate acid are associated with increased CV and all-cause mortality, also in over 65-year-olds. Especially hyperuricemia increases the risk of mortality, but the association is U-shaped (Tseng et al., 2018).

Hypocalcemia may be associated with increased mortality, especially in the older population with comorbidities (Xu et al., 2025).

An increased mortality rate has been observed in older individuals with thyroid dysfunction. The level of thyroid stimulating hormone increases with healthy ageing, which is important to note in diagnosing thyroid disorders in older people (Mitrou et al., 2011).

There is also some evidence on the association of ferritin, which is both a critical protein in iron homeostasis, low in iron deficiency, and an acute phase inflammatory marker, with mortality (Ellervik et al., 2014; Mahroum et al., 2022).

Increased serum alkaline phosphatase levels have been linked with increased all-cause mortality in general population, and alanine aminotransferase levels also in older population (Schmilovitz-Weiss et al., 2018; Yan et al., 2023).

The somewhat controversial role of LDL cholesterol in the older population has been discussed in the chapter of CVD risk factors.

6.2.1.2 Laboratory parameters in prediction of institutionalization

Clinical FIs have been shown to predict institutionalization (Rockwood & Mitnitski, 2007), also in our study population (Viljanen et al., 2021), but the LI did not. This finding can be considered logical as the most common causes of institutionalization, dementia and cognitive impairment, cannot be predicted by routine laboratory testing (Bharucha et al., 2004; Gnjidic et al., 2012; Luppa et al., 2010; Salminen et al., 2017, 2020; von Bonsdorff et al., 2006). The same applies for some other factors that are known to predict institutionalization, impairing an older person's ability to live independently; increased falls, decreasing body mass index (Salminen et al., 2017, 2020) and functional impairment and disabilities, especially when combined with cognitive impairment (Gnjidic et al., 2012; Luppa et al., 2010; von Bonsdorff et al., 2006). A systematic review on laboratory-based indexes found an association of a laboratory-based index with institutionalization in one study, but not in another study apart from our study (Hakeem et al., 2023). In the study where there was an association between the laboratory-based index and institutionalization, it was weaker than for the clinical FI. Also, their index included blood pressure and pulse in addition to laboratory parameters (Blodgett et al., 2016).

6.2.2 Combined indexes (Study II)

As clinical and laboratory-based indexes measure frailty differently, it could be ideal to combine both to acquire the most accurate predictive ability. We created an index that combines our clinical and laboratory indexes that had both been studied independently. Both had been found to predict mortality in our population cohort, and the clinical FI also institutionalization. The clinical data included deficits that reflect several aspects of the person's health status such as mobility, daily functions and diagnosed diseases.

In addition to the LI+FI with all the fourteen laboratory and fifty clinical parameters, we used a statistical method to find a combination of a few parameters

that best predicted mortality and institutionalization out of the large number of variables. This way we could create indexes that take little time to implement and still have a good predictive ability.

6.2.2.1 Prediction of institutionalization

The LI+FI was not better for predicting institutionalization compared to the clinical FI alone that was studied in a previous study on the same population (Viljanen et al., 2021). After implementing the statistical method to reduce the number of parameters to only those that showed the best predictive value, no laboratory parameters were left in the index predicting institutionalization, which is consistent with the result that the LI could not predict institutionalization.

The three parameters that remained in the reduced index for institutionalization were need for help with preparing meals, need for help with heavy household chores, and need for help with moving about inside the house. Being able to prepare meals independently is one of the instrumental activities of daily living, that reflect the person's ability to carry out daily activities, and their cognitive function. Earlier studies have shown dependence in daily activities to be a predictor of morbidity and mortality in older populations (Millán-Calenti et al., 2010). Need for help with moving about inside house is also consistent with the earlier finding that self-reported walking ability predicts a person's risk for institutionalization (Viljanen et al., 2021).

6.2.2.2 Prediction of mortality

The LI+FI was better at predicting mortality than the clinical FI or the LI alone. The clinical parameters left in the reduced index as predicting factors for mortality were need for help with preparing meals, limited kind of amount of activity, need for help with heavy household chores and difficulties carrying or lifting light loads. Two of them reflect the physical capacity of the person. Many studies have found physical activity to have a positive effect on health and to reduce mortality (Hupin et al., 2015; Lear et al., 2017). Limited kind of amount of activity was a predicting factor for mortality and refers also to other than physical activity, including interests and hobbies. In addition to these, diabetes and heart disease were left as predicting factors in the index predicting mortality.

The laboratory parameters that were found most significant in predicting mortality and were left in the reduced index were hemoglobin, CRP and sodium, all independently associated with mortality according to previous studies (Corona et al., 2013; Culleton et al., 2006; Hupin et al., 2015; Lear et al., 2017; Li et al., 2017; Millán-Calenti et al., 2010; Shavelle et al., 2012).

6.2.2.3 The predictive value of the combined and the reduced indexes

The results showed that a large index with fifty parameters included many unnecessary parameters that did not increase its predictive value and therefore could be replaced with a reduced index with only a few carefully chosen parameters that were individually associated with institutionalization or death. The reduced indexes had even a slightly better predictive ability in comparison with the 50-parameter combined index. These indexes with only a few clinical questions in addition to three basic laboratory tests would take very little time in a doctor's appointment and thus could be used to screen older people. This kind of short intervention could be done during any health care contact with an older person. The indexes could also potentially be calculated automatically if the necessary information was collected in the electronic patient records similarly to electronic FIs that are automatically populated from routine collected data contained within the electronic patient records (Clegg et al., 2016).

6.2.3 Reference limits for troponin T and N-terminal b-type natriuretic propeptide in older population (Study III)

Comorbidities are especially common among older population, which complicates the definition of reference limits in this population. In accordance with previous studies we found that cTnT and proBNP concentrations are higher in older population without any cardiac symptoms or diagnosis of a cardiac disease when compared to general adult population (Cardinaels et al., 2015; Costello-Boerrigter et al., 2006; de Lemos et al., 2010; Fradley et al., 2011; Franzini et al., 2015; Galasko et al., 2005; Goudot et al., 2021; Li et al., 2015; Menacer et al., 2013; Nadrowski et al., 2013; Olivieri et al., 2012; Reiter et al., 2011; Wu et al., 2018; Zhang et al., 2020). In our study population the concentrations of cTnT were higher in older men in comparison with older women in all age groups, as most other studies have found as well (de Lemos et al., 2010; Olivieri et al., 2012; Zhang et al., 2020). Women had higher concentrations of proBNP as in earlier studies (Costello-Boerrigter et al., 2006; Fradley et al., 2011; Galasko et al., 2005).

We established reference limits for cTnT and proBNP for older people to help decision-making in clinical settings. We chose those individuals with no diagnosed renal diseases or CVDs for the reference population instead of requiring the individuals to be without any illnesses. This is both much easier to implement and closer to the situation in real life.

6.2.3.1 Cardiac troponin T

Especially the median cTnT values in our population with a previous heart disease were close to the cut-off of 14 ng/L recommended by the manufacturer to rule-out AMI, even though none had acute symptoms at the time of the initial examination. The established reference limits were higher than 14 ng/L in each age group and increased with age.

Misdiagnosis causes harm both for the individual and the society. Overdiagnosis is an important issue that may nowadays be the most important issue when considering the diagnostics of AMIs because of more sensitive diagnostics of troponin rise. Even if no AMIs should be missed, the costs with overdiagnoses are non-negligible, and the resources could be used for alternative health benefits (McCarthy et al., 2024, Eggers et al. 2009). The improved laboratory diagnostics that enable us to find many more patients with positive test results than previously with the simultaneous increase in life expectancy and the percentage of older population brings new challenges, making it ever more important to apply appropriate reference ranges for persons with different ages.

6.2.3.2 N-terminal b-type natriuretic propeptide

The reference limits we established for proBNP in our population increased significantly with age. There are several threshold levels that are used for proBNP, such as the National Institute for Health and Care Excellence guideline of 400 ng/L likely to rule out heart failure, and the European Society of Cardiology guideline that recommends further investigation at proBNP levels above 125 ng/L in the non-acute setting, and above 300 mg/L in acute settings (Ponikowski et al., 2016; National Guideline Centre (UK), 2018). According to the manufacturer of the proBNP assay the levels of proBNP rise with increasing age, and in their reference group from the Gutenberg Health study there was a 97.5th percentile value of 879 ng/L for men aged 65 to 74 years and 623 ng/L for women aged 65 to 74 years in a population with no prevalent CVD (Tzikas et al., 2013). The 97.5th percentile values in our population were lower (272, 287, 373 and 686 ng/L for men depending on the age group, and 341, 377, 471 and 794 ng/L for women). There is a large variation between the thresholds recommended by guidelines.

6.2.3.3 Age groups

As cTnT and proBNP levels clearly increase with ageing, we defined separate reference ranges for age groups 64 to 69-year-olds, 70 to 74-year-olds, 75 to 80-year-olds, and for 80-year-olds and older. The concentrations of both cTnT and proBNP seem to rise with advancing age also after the age of 80 but the dispersion in the

population gets larger. This might be due to more underlying asymptomatic heart conditions in the oldest old population even if in our study all participants were carefully examined to exclude all persons with any signs or symptoms of a cardiac disease so that only 60.5 percent of the initial population formed the reference group. The possibility remains that some individuals had asymptomatic cardiac conditions that were not diagnostic at the time of the baseline examination, but these undiagnosed underlying heart conditions were at a stable stage at the time. As this might be a more relevant problem in the eldest group with more dispersion, we suggest using the reference limits of over 80-year-olds for all persons over the age of 80, even if it is likely that the reference limits continue to rise with advancing age.

6.2.4 Prediction of cardiovascular events and cardiovascular and all-cause mortality with troponin T and N-terminal b-type natriuretic propeptide (Studies III and IV)

We studied if elevated cTnT of proBNP could predict future AMIs in our study participants who already had a diagnosis of a heart disease at baseline.

Participants with a heart disease and an elevated cTnT level were more likely to have a new AMI, and only three of those were both alive and did not have a new AMI by the end of the follow-up period suggesting that a person with a previous heart disease and an elevated cTnT level is at a significant risk of a new AMI and death. It is nevertheless important to note that most of those who had a new AMI, had a level of cTnT at baseline which was inside our newly established reference limits. This finding suggests that while those with an elevated cTnT level are at higher risk, lower cTnT level cannot rule out a future risk for an AMI.

Elevated proBNP level was very common in patients with a previous diagnosis of a heart disease. Elevated levels of proBNP have been shown to predict CV events and mortality in older people with or without heart failure and also after AMI (Lorgis et al., 2009; Wang et al., 2004). In our study the participants with an elevated level of proBNP were more likely to have an AMI both among participants with and without a previous diagnosis of a heart disease. The results suggest that the levels of both cTnT and proBNP reflect the health status of the heart even when no acute symptoms are present.

The results are in accordance with previous research. Both studied cardiac biomarkers have been found to predict incident coronary heart disease, also in a multiethnic population without known CVD and independent of established risk factors and ethnicity. The Multi-Ethnic Study of Atherosclerosis also found that adding a baseline proBNP improved the risk discrimination of established CV risk scores, the Framingham Risk Score and the Pooled Cohort Risk Equation for estimation of 10-year CVD risk. In this study, proBNP predicted incident CVD also

independently above these risk scores. The use of proBNP on top of clinical risk factors resulted in a net 20% improvement in the classification of CVD risk (Daniels et al., 2015).

Risk models based on traditional risk factors provide only moderate discrimination of a person's risk for CV events, and especially for those with an intermediate risk score (Leong et al., 2025). Identifying and integrating other factors that include circulating biomarkers could improve risk assessment accuracy and strengthen primary prevention efforts.

Emerging research indicates that the levels of cTnT, proBNP and also CRP in the general population may indicate subclinical heart damage and adverse cardiometabolic health, providing further insights into an individual's long-term CVD risk (Neumann et al., 2025). These biomarkers have been shown to have incremental value when adding them into models containing established risk factors (Neumann et al., 2024; Westermann et al., 2017; Willeit et al., 2017). While the predictive value of conventional risk factors seems to attenuate in older people, the added value of cTnT or proBNP in risk estimation seems to be largest in older people (Neumann et al., 2024). In our study, the CV and all-cause mortality were higher in participants with concentrations of cTnT or proBNP at the highest quartile compared with those in the lowest quartile, although statistical significance was not reached in all groups. Our results suggest that the concentrations of both cTnT and proBNP reflect the cardiac health status, even in the absence of acute symptoms.

Age obviously plays a major role in the mortality of older adults, which is why analyses in age groups and adjustments with age are important. In our study, the associations of higher cTnT and proBNP concentrations with both CV and all-cause mortality remained. The associations were mostly stronger in the older group of over 75-year-olds than in the younger age group. Overall, the associations were stronger for CV mortality.

6.3 Strengths and limitations

The strengths of this study include the large sample size, good participation rate of 82%, and a long follow-up period that enable broad generalizability of the results. The data comes from a community-based representative sample of the Finnish population.

In the first study on the LI, we used two follow-up periods of 10 and 18 years, which can be considered especially long, as it was the longest follow-up period in a review of 38 studies on laboratory-based indexes (Sapp et al., 2023).

In the analyses regarding institutionalization, there was missing data for those who no longer lived in Lieto at the end of the study. Also, persons still living at home after the follow-up period were considered not institutionalized, which can be

considered a limitation since some of them can still be institutionalized during their lifetime. Other than these limitations, the data for the outcomes can be considered reliable. The dates for institutionalization were gathered from electronic patient systems which is more exact compared to earlier studies in which the information was gathered by interview (Hajek et al., 2015; Bravell et al., 2009). The data for mortality is reliable as all deaths in Finland are registered in the Official Finnish Cause of Death Registry. The diagnoses were collected from multiple data sources: the municipality's electronic patient record system, the Finnish Hospital Discharge Register, and the Finnish Cause of Death Registry.

Since the data was cross-sectional, we were unable to investigate if subclinical deficits were detectable prior to clinical ones.

The clinical parameters in the combined FI+LI were from a previously validated FI that consists of parameters describing a person's functional abilities and some chronic diseases. It can be considered a limitation to the study that the index does not contain some other factors that also alter a person's risk, such as cigarette smoking or body mass index. These factors have typically not been directly included in indexes that assess frailty but can also contribute to a person's risk for mortality and other adverse outcomes. Nevertheless, these factors may have caused diseases that are included in the index. The laboratory parameters for the LI were chosen based on an educated guess so that they would be informative of the state of various organ systems and easily obtainable in clinical use, but we did not study how the inclusion of other laboratory parameters would have altered the predictive ability of the index.

All the parameters were classified as binary variables as a person either having or not having a certain deficit without considering how abnormal the result was. The laboratory parameters were classified as either inside or outside reference ranges and not as continuous variables. A certain value is considered normal of abnormal depending on the chosen reference ranges. Those with a value close to the cut-off limit are classified as having a certain deficit or not, although a single value close to the cut-off limit may be due to normal variation. The inclusion of multiple parameters in the indexes lessens the effect of a single laboratory value, but especially in the reduced indexes, the effect of single parameters classified as normal or abnormal is larger. We did not separate if the value was below or above the normal range. This simplifies the clinical usage of the index as both low and high values are considered abnormal, even if naturally they implicate different disease states. While this approach does not provide information on the pathology causing the laboratory abnormality, it is typical in indexes that predict frailty and other non-disease-specific states.

All the created indexes should be validated in another population.

The reference ranges for cTnT and proBNP were defined from a community-based representative sample of older population. The sample size was relatively large, even if the oldest age groups of men and women were smaller which is often a challenge when establishing reference ranges for older population.

cTnT and proBNP were measured only at one time-point at baseline. The health status of the participants was based on a clinical examination by a physician, patient health records and a comprehensive interview but cardiac imaging was not performed for the reference population. We formed the reference population with individuals without symptoms and with no known heart conditions. Diagnosed cardiac conditions are common in older population but possibly also undiagnosed underlying cardiac conditions which may cause dispersion in the concentrations of cTnT and proBNP, especially in the oldest. It is reasonable to assume that potential hidden undiagnosed co-morbidities may impact the reference ranges, and coronary artery disease cannot be excluded without angiographic examination. Increased cTnT levels may be detected in conditions other than acute ischemia such as inflammation of the heart, endothelial dysfunction, micro-vascular disease or left ventricular strain (Agewall et al., 2011; Askin et al., 2020).

It is possible that also the increase in all-cause mortality that we found in our study with high cTnT and proBNP levels, is partly related to undiagnosed and untreated myocardial damage that might increase the likelihood of non-CV death. Renal function is important in metabolism and removal of both biomarkers (Chaulin, 2022; Martinez-Rumayor et al., 2008), and therefore underlying decreased kidney function may influence the concentrations of cTnT and proBNP, although in this study the individuals with kidney diseases at baseline were excluded.

cTnT presents in different forms in plasma due to its degradation. Intact and long forms of cTnT are detected early after AMI, and truncated smaller fragments of cTnT in myocardial injury attributable to other causes. The heavily truncated fragments may be responsible for chronic cTnT elevations as seen for example in renal dysfunction (Cardinaels et al., 2013; Aalto et al., 2026; Airaksinen et al., 2022; Mingels et al., 2017). The commercial cTnT assay that was used to define cTnT levels in our study measures all forms of cTnT so we could not separate if the participants' cTnT elevations were caused by intact or fragmented forms of cTnT. Separation of the different forms of cTnT could have brought more insight on the causes of the elevations of cTnT levels even though participants with a renal dysfunction were not included in the study. Also, we did not study macro troponins that could have resulted in increased concentrations of cTnT in some individuals.

All the laboratory parameters were measured at one time point. A serial measurement might improve the predictive value of the biomarkers, as was found on a study on proBNP, where a significant rise or drop of at least 25 percent in three years was associated with an increase or a decrease in the incidence of CVD,

respectively (Daniels et al., 2015). A similar result was found earlier in older adults in the Cardiovascular Health Study (deFilippi et al., 2010).

6.4 Implications for clinics and future research

6.4.1 Implications for clinics

In clinical settings, the implementation of an index consisting of available routine laboratory data may be easier and more harmonized than using data based on clinical assessment. Some of the risk factors that can be identified by laboratory tests can be treated when found early enough. Others reflect a person's health status but cannot be treated as such. For example, a decreased or an elevated sodium level is not a disease-specific finding, but as part of an index can be indicative of an increased risk. An elevated CRP level indicates silent inflammation and the risk for atherothrombosis and ischemic heart disease (The Emerging Risk Factors Collaboration, 2012; Giovannini et al., 2011; Kistorp et al., 2005). Elevated levels of cTnT and proBNP indicate an increased risk for CVD and mortality, and even if ways to lower their levels are limited, their elevated levels indicate a need to affect other treatable risk factors for CVD.

Using the LI would not be time-consuming or expensive; it could serve as an alert for the clinician to pay attention to those patients with a high index score. A laboratory-based index is an objective approach for assessing frailty with easy interpretation. Apart from the smaller than normal number of deficits, the LI that was created as part of this thesis fulfills the criteria that is generally considered when creating a FI: the variables are diverse, representing different aspects of health, they are scored 0 or 1, their prevalence increases with age, reflecting deterioration of health, but they do not saturate so that every person at old age would have a certain deficit.

On the other hand, a combination of clinical and laboratory parameters might be an optimal solution for the most comprehensive assessment of an older individual's frailty status. An index with a small number of parameters could be practical to use as part of an older person's any health care visit; in a health check-up, emergency care, or when planning follow-up care after a hospital stay or a surgery. In large indexes, some parameters, such as the different activities of daily living, may correlate significantly with each other, and thus, their number can be reduced without compromising the predictive ability of the index.

Identification of increased risk may aid in assessing the health status of an older person, and planning their health interventions, although the right interventions must be considered on an individual basis. A person's cTnT and proBNP concentrations must be interpreted in connection with the person's age, overall health status, and

existing health conditions. Interventions directed at treating those with elevated cTnT or proBNP levels may reduce morbidity and mortality from CV and other causes.

The important question is how to treat a patient after defining their index score. The aged population is very diverse, and individuals with the same chronological age might have a very different biological age. The indexes could aid in defining the individual's condition that is not based on their chronological age. This could help in targeting interventions, building an individual care plan, and considering which treatments are appropriate for the individual. The parameters of the clinical FIs are mostly descriptive of a person's functional status. When a person already has disabilities, primary prevention is late but further decline can still be affected and there is evidence that an FI score can also improve (He et al., 2025; Mitnitski et al., 2012; Ng et al. 2015). The idea behind laboratory-based indexes is to detect also subclinical defects before their clinical manifestations and thus they could possibly be used also in prevention of clinical defects. Sometimes underlying diseases causing laboratory defects may be found. The index score helps to identify those at high risk, and then to target interventions to delay adverse outcomes, even if the individual parameters cannot always be treated.

Assessing the prognosis of geriatric patients is essential for clinicians to balance the potential risks and benefits of available treatment options. The index score could aid in determining the possible benefit that an individual may gain from medications that reduce the risk for certain illnesses such as lipid-lowering or anti-thrombotic medications. It may be uncertain if a very frail person benefits from a medical intervention, such as a medication that reduces a risk that might actualize in a few years. A very high index score could aid in determining if aggressive examinations or treatments are sensible when an individual's life expectancy is short.

There are still no ready answers to questions on what index score a person must have to be suitable for a certain intervention or treatment. Lifestyle intervention may be considered at any age. There is evidence on the benefits of lifestyle changes such as smoking cessation or increasing physical exercise also in old age. Probably the biggest issue is how to motivate a person to change their habits. The finding that the FI scores can also improve indicate the abilities of organisms to repair (He et al., 2025; Mitnitski et al., 2012). Physical, nutritional, and cognitive interventions can aid in reversing frailty (Ng et al., 2015).

Frailty is closely connected to CVD. Screening for frailty status is important also to prevent CVD as CV events contribute significantly to disability and mortality in older people. Frailty increases vulnerability to adverse CV events. On the other hand, the CV system affects the health of all systems of the organism and its defects predispose the person to frailty. Also, many of the risk factors for these conditions are the same. Interventions that could be used for treating frailty, such as increasing

physical activity and nutritional interventions, are also useful for preventing the onset of CVD (Strandberg & Nieminen, 2020; Veronese et al., 2017). The ESC guideline from 2021 recognizes a gap of knowledge on management of CVD risk in older people over 85 years of age, although cessation of smoking and increasing physical activity are considered important (Visseren et al., 2021).

CVD is also a major risk factor for the development of dementia, and treating the modifiable risk factors for CVD also contributes to the prevention of dementia (Kauko et al., 2024). Assessment of a person's risk for CVD is essential to reduce CV events, dementia, institutionalization and mortality, and to increase functional life years. In Finland, both CVD prevalence and mortality have decreased because of improved life habits and better prevention and treatment of risk factors, and treatment of CVD (Jousilahti et al., 2016). Nevertheless, the increasing older population and improved treatment may increase the global prevalence of coronary artery disease and other CVDs in the future.

This study confirmed that cTnT and proBNP can be used in screening for long-term CVD and mortality risk of older people and identifying a subgroup of older people that need health care interventions. Baseline concentrations of cTnT and proBNP were higher in older population than in younger population without CVDs, which complicates the diagnostics in acute situations. Using age-adjusted reference limits may be useful to improve the diagnostics of CVDs. The application of separate reference limits for older population would have clinical implications, considering the high prevalence of older patients in emergency care as well as in other health care appointments. Troponin levels are often examined with admittance of an older person in an emergency room, and it is important to notice that it is quite likely that they may have their cTnT levels higher than the conventional cut-off limit of 14 ng/L also without an acute ischemic disease. When the reference limits that are established for general adult population are used for older people, their higher cTnT and proBNP concentrations may cause overdiagnosis and lead to unnecessary examinations and treatments. In older patients with elevated levels of cTnT, the change in cTnT concentrations between two following samples is of clinical significance in acute situations, but less follow-up samples and unnecessary monitoring at emergency care are needed when the initial cut-off limits are more appropriate for the population. Even if follow-up samples are still needed when an older person presents with acute cardiac symptoms, it is important to understand that their baseline cTnT level may be over the conventional cut-off limit unrelated to the acute symptoms.

6.4.2 Implications for future research

By using a statistical method to reduce the number of parameters of the combined clinical and laboratory index, starting from fifty, they were reduced to nine for the

mortality prediction index, and three for the institutionalization prediction index. This very significant reduction of parameters could be done without compromising the predictive ability of the combined indexes. The parameters for the LI were selected so that they would mostly reflect the health status of different organ systems. Nevertheless, it is possible that all of the fourteen parameters are not necessary, and their number could still be reduced. There is some evidence on the predictive value of each of the fourteen analytes for mortality, at least in some settings, but it may be that all these parameters are not necessary to include in the index. Also, our LI included LDL cholesterol whose predictive role in the mortality of older population is not clear. For example, it would be interesting to see how well a combination of only hemoglobin, sodium and CRP, that were the only laboratory analytes left for the reduced combination index, predicts mortality.

In this thesis, mortality and institutionalization were used as outcomes in the index studies, and CV events, CV mortality, and total mortality in the cardiac marker studies. As the main goal is to increase healthy and functional life years, it would be useful and interesting to test how these newly-created indexes predict other outcomes, and to find early indicators for functional decline in future research.

The new reference ranges for cTnT and proBNP should be tested in another population of people aged 65 years and older.

7 Conclusions

This thesis shows that older population free of heart and kidney diseases have higher levels of cTnT and proBNP compared to general adult population and thus we suggest using separate reference limits for older population. The new suggested reference limits divided in four age groups for men and women should be validated in another population of older people. Using these new cut-off limits, elevated proBNP was associated with the occurrence of AMIs in older population with and without a previous diagnosis of a heart disease during a 10-year follow-up period. Older people with higher cTnT and proBNP concentrations have an increased risk of CV and all-cause mortality, even when they do not indicate an acute CV event. Acknowledging the elevated risk may aid in targeting follow-up, prevention, and treatment adequately and more individually.

Findings of this thesis show that a practical index based on 14 routine laboratory tests can be used to predict mortality among older people. The number of routine laboratory test results outside reference ranges correlates with older people's mortality. A laboratory-based FI could be an easily applicable screening instrument in clinical settings. Laboratory and clinical deficits can also be combined to form an index to predict an individual's risk for mortality, which may be the optimal solution because clinical and laboratory deficits provide different information. Nevertheless, laboratory parameters cannot aid in prediction of institutionalization. According to this thesis a large number of parameters, as typically included in clinical and laboratory-based FIs, is not necessary, and their number could be significantly reduced by statistical methods without compromising the predictive ability of the indexes.

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