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LIST OF ABBREVIATIONS

ACE2	angiotensin-converting enzyme 2
aHR	adjusted hazard ratio
aOR	adjusted odds ratio
ARDS	acute respiratory distress syndrome
aRRR	adjusted relative risk ratio
BTI	breakthrough SARS-CoV-2 infection
cIR	crude incidence rate
CFR	case fatality ratio
CKD	chronic kidney disease
COVID-19	coronavirus disease 2019
CT	computed tomography
ECDC	European Centre for Disease Prevention and Control
ED	emergency department
EID	emerging infectious diseases
EHIF	Estonian Health Insurance Fund
HIV-1	human immunodeficiency virus type 1
ICU	intensive care unit
IDSA	Infectious Diseases Society of America
IR	incidence rate
LNP	lipid nanoparticle
MACE	major acute cardiovascular events
ME/CFS	myalgic encephalomyelitis/chronic fatigue syndrome
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
MIS-A	multisystem inflammatory syndrome in adults
MIS-C	multisystem inflammatory syndrome in children
NAFLD	non-alcoholic fatty liver disease
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
PIM	post-infectious mortality
RBD	receptor binding domain
RNA	ribonucleic acid
RSV	respiratory syncytial virus
SARS-CoV	Severe Acute Respiratory Syndrome Coronavirus
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SMD	standardized mean difference
TIA	transient ischemic attack
TTE	target trial emulation
VE	vaccine effectiveness
VOC	variant of concern
wIR	weighted incidence rate
wIRR	weighted incidence rate ratio
WHO	World Health Organization

LIST OF ORIGINAL PUBLICATIONS

Publications included in the thesis:

I. Meister T, Pisarev H, Kolde R, Kalda R, Suija K, Milani L, Karo-Astover L, Piirsoo M, Uusküla A. Clinical characteristics and risk factors for COVID-19 infection and disease severity: A nationwide observational study in Estonia. PLoS One. 2022 Jun 16;17(6):e0270192. doi: 10.1371/journal.pone.0270192.

II. Meister T, Kolde A, Fischer K, Pisarev H, Kolde R, Kalda R, Suija K, Tisler A, Uusküla A. A retrospective cohort study of incidence and risk factors for severe SARS-CoV-2 breakthrough infection among fully vaccinated people. Sci Rep. 2023 May 26;13(1):8531. doi: 10.1038/s41598-023-35591-w.

III. Meister T, Maiväli Ü, Tenson K, Tisler A, Kalda R, Suija K, Uusküla A. Dynamic effects of COVID-19 vaccination on major acute cardiovascular events and mortality following SARS-CoV-2 infection in a target trial emulation study. Sci Rep. 2025 Jul 29;15(1):27530. doi: 10.1038/s41598-025-13043-x.

The author's personal contribution:

Study I: Study design, interpretation of results, analysis, drafting the manuscript, to which the authors contributed and approved the final manuscript.

Study II: Study design, interpretation of results, analysis, drafting the manuscript, to which the authors contributed and approved the final manuscript.

Study III: Study design, interpretation of results, analysis, drafting the manuscript, to which the authors contributed and approved the final manuscript.

1. INTRODUCTION

The Coronavirus Disease 2019 (COVID-19) pandemic, declared a global health emergency by the World Health Organization (WHO) in March 2020, has profoundly disrupted health systems, economies, and societies worldwide. In its early stages, public health efforts were primarily directed toward reducing mortality and curbing the transmission of SARS-CoV-2. However, it soon became evident that the virus could lead to a broad spectrum of long-term health consequences, including cardiovascular complications and persistent symptoms now collectively referred to as post-acute sequelae of COVID-19, or long COVID.

The initial rollout of COVID-19 vaccination programs across Europe, including Estonia, encountered numerous challenges, including limited vaccine supply, logistical constraints, communication barriers, and vaccine hesitancy, which hindered efforts to achieve rapid and equitable vaccine coverage.

During the initial stages of the COVID-19 pandemic, the escalating pressure of overwhelmed healthcare systems and profound uncertainty – amid scarce real-world evidence – necessitated the development of prioritization frameworks to allocate vaccines efficiently. These frameworks relied on factors such as age, comorbidities, and occupational risk, primarily informed by early observational data drawn from limited cohorts of severely ill COVID-19 patients. A particular role was assigned to primary health physicians in implementing these frameworks, identifying high-risk individuals, managing chronic conditions amidst a raging pandemic, and serving as trusted sources of guidance for their patients amidst a relentless influx of rapidly changing information, scientific updates, and public health directives.

As the pandemic progressed and vaccine availability improved, new questions emerged regarding the durability of vaccine-induced immunity, the risk and severity of breakthrough infections, and the potential of vaccination to mitigate long-term complications of COVID-19.

Vaccination has become the cornerstone of prevention, with strong evidence supporting its effectiveness in reducing severe COVID-19 and deaths. While initial studies often suffered from selection bias and limited generalizability, the importance of conducting large-scale, population-based, real-world cohort studies became increasingly evident to understand the full spectrum of COVID-19 outcomes and the impact of vaccination.

To address these knowledge gaps, this dissertation presents findings from three nationwide cohort studies using data from Estonia's electronic health databases. The research employs methodological progression from traditional regression-based models to target trial emulation (TTE), enhancing the ability to draw causal inferences from observational data in a real-world setting.

This dissertation explores how COVID-19 vaccination has influenced infection risk and disease severity across diverse population groups. It places particular emphasis on the long-term health consequences of SARS-CoV-2 infection, focusing on the role of pre-infection vaccination in reducing major acute cardio-

vascular events (MACE) and all-cause mortality. Special attention is given to the time-dependent effects of vaccination within the broader context of long COVID, contributing to a more comprehensive understanding of the extended benefits of vaccination beyond the acute phase of COVID-19.

2. REVIEW OF THE LITERATURE

2.1 Novel SARS-CoV-2 coronavirus

In December 2019, a cluster of pneumonia cases of unknown origin emerged in Wuhan, China (Phelan et al., 2020). The World Health Organization (WHO) was notified on December 31. Within a week, scientists identified the novel coronavirus – 2019-nCoV – and shared its genetic sequence globally, enabling the rapid development of diagnostic tools (C. Wang et al., 2020; WHO, 2020b; Y.-Z. Zhang & Holmes, 2020). Despite early containment efforts launched by the Chinese government, SARS-CoV-2 quickly spread to neighboring countries, prompting the WHO to declare a Public Health Emergency of International Concern on January 30, 2020 (WHO, 2020c). This was followed by the official naming of the virus as *Severe Acute Respiratory Syndrome Coronavirus 2* (SARS-CoV-2) and the disease as COVID-19 on February 11 (CDC, 2023; WHO, n.d.-b). The pandemic was formally declared on March 11, 2020, prompting unprecedented public health measures worldwide to prevent the healthcare system from collapsing due to the outbreak of severe COVID-19 cases (WHO, 2020e). The WHO played a central role in coordinating the global response by launching a medical information system, living guideline, and standardizing disease terminology (WHO, n.d.-a). Soon after, other internationally influential organizations, such as the National Institute for Health and Care Excellence (NICE) and the European Centre for Disease Prevention and Control (ECDC), issued guidelines to manage COVID-19, a disease that has since reshaped global health, economic, and social systems (ECDC, 2020; NICE, 2021).

SARS-CoV-2 is a highly contagious, positive-sense ribonucleic acid (RNA) virus from the *Coronaviridae* family, with a large genome encoding proteins that enable viral entry, replication, immune evasion, and host gene suppression (C. Bai et al., 2022). There has been limited research so far on the epidemiology of coronaviruses until the outbreak of highly deadly coronaviral mutant severe acute respiratory syndrome coronavirus (SARS-CoV) in China in 2002 and Middle East respiratory syndrome coronavirus (MERS-CoV) in the Kingdom of Saudi Arabia in 2012, both belonging to coronaviruses and having extremely high rates of death in infected individuals (9.5 and 35.5%, respectively) (V. C. C. Cheng et al., 2007; Drosten et al., 2003; Memish et al., 2020; Tyrrell & Myint, 1996).

Most RNA viruses that infect humans originate from animals. Some of these zoonoses have adapted to humans (i.e., Human Immunodeficiency Virus type 1 (HIV-1), SARS-CoV, and dengue virus), while others (i.e., zoonotic Influenza A viruses) have either remained zoonotic spillovers or disappeared over time due to a lack of ability to sustain human-to-human transmission (Kessler et al., 2021; Woolhouse et al., 2013). RNA viruses adapt rapidly to new hosts due to frequent mutations caused by their error-prone RNA polymerase. A single strain can quickly generate diverse variants, evolving thousands to millions of times faster than DNA viruses, which typically cause long-term infections with great adaptation, such as embedding into the host genome (i.e., Human Papillomavirus HPV,

HIV) (Irwin et al., 2022; Szpara & Van Doorslaer, 2021; Villa et al., 2021). New RNA viruses are most likely to emerge in regions that combine high human population densities with high densities of domestic animals or a high diversity of wildlife. SARS-CoV-2 is not the only novel virus of the past century. Between 1940 and 2004, researchers identified approximately 335 emerging infectious diseases (EIDs), including newly evolved strains of known pathogens, infections entering human populations for the first time, and historically present but re-emerging pathogens. Zoonoses represent the vast majority of EID (Jones et al., 2008). Over 99% similarity in key genes between bat and human coronaviruses, along with the cross-species adaptability of spike protein (S-protein), supports theories of SARS-CoV-2's zoonotic origin (Graham & Baric, 2010; Tiwari & Mishra, 2020).

It is well known now that SARS-CoV-2 shares significant genomic and phylogenetic similarities with SARS-CoV in the receptor binding domain (RBD) of S-protein (Naqvi et al., 2020; F. Wu et al., 2020), and with SARS-CoV and MERS-CoV in essential enzymes and structural proteins, while revealing some differences in virus invasion mechanism (Naqvi et al., 2020). While MERS-CoV uses the dipeptidyl peptidase 4 receptor for invasion, SARS-CoV-2 and SARS-CoV use the Angiotensin-Converting Enzyme 2 (ACE2) receptor for cell entry (Jones et al., 2008; Shirbhate et al., 2021; H. Zhang et al., 2020). ACE2 receptors are widely distributed in the human body, with abundant presentation in the gut cells, endothelial and smooth cells of the blood vessels, heart myocytes, coronary arteries, bronchial cells and pneumocytes, brain cells, genitourinary system cells, and on tubular epithelial cells of the kidney (Shirbhate et al., 2021). Unlike its predecessors, SARS-CoV-2 achieves high viral loads in the upper respiratory tract even in asymptomatic or mildly symptomatic individuals, enabling it to cause explosive and often undetected transmission, making the rollout of the pandemic inevitable (Zumla & Niederman, 2020).

Since the start of the pandemic, SARS-CoV-2 has undergone numerous mutations, leading the WHO to designate five main variants of concern (VOC) – Alpha, Beta, Gamma, Delta, and Omicron – named sequentially using the Greek alphabet to ensure a sequential way to name variants as they emerge, facilitate clear communication, and avoid geographic stigmatization. These variants were selected based on their ability to cause more severe disease, increase transmissibility, or reduce the effectiveness of public health measures and vaccination (WHO, n.d.-c).

A characteristic feature of seasonal coronaviruses, such as HKU1, NL63, OC43, and 229E, is the lack of long-lasting immunity, allowing individuals to become reinfected, sometimes within a year (Edridge et al., 2020). Similarly, acquired immunity against SARS-CoV-2 seems to be attenuated soon after primary infection. However, some differences exist between pre-Omicron and post-Omicron estimates of protection against reinfection, with earlier variants providing more durable immunity (lasting approximately one year). In contrast, Omicron-induced immunity tends to wane more rapidly (Chemaitelly et al., 2025).

The case fatality ratio (CFR) is a commonly used metric for gauging disease severity and navigating healthcare responses during pandemics. For COVID-19, a systematic review encompassing data from the first year of the pandemic estimated an overall pooled CFR of 10%, with notable differences: 1% in the general population, 13% in hospitalized patients, and 37% among individuals hospitalized in intensive care units (ICU). Most studies focused on hospitalized patients, with mild cases underrepresented due to testing policies, potentially overestimating the actual fatality rate (Alimohamadi et al., 2021). Later meta-analysis incorporating studies up to March 2023 found the Beta SARS-CoV-2 strain showed the highest CFR (4.2%) and Omicron the lowest (0.7%). Key influencing factors included age, vaccination coverage, human development index, and healthcare capacity of the region, with higher CFRs for older populations and those with lower vaccination rates (Xia et al., 2024). A nationwide study conducted in Estonia found that Omicron clades were associated with significantly lower hospitalization rates compared to earlier SARS-CoV-2 variants, independent of sex or vaccination status (Päll et al., 2024).

Given the wide variability in reported CFR for COVID-19 across studies and the limited understanding of factors influencing its severity, real-world evidence from national settings is essential to contextualize global estimates with locally relevant data.

2.2 COVID-19 pandemic milestones and vaccination in Estonia

The Estonian government officially declared a state of emergency on March 12, 2020, due to local transmission of SARS-CoV-2 infection, identified through real-time polymerase chain reaction (PCR) testing of nasopharyngeal specimens – the method widely implemented then alongside rapid antigen testing for confirming COVID-19 cases (Riigi Teataja, 2020). PCR testing is a highly specific molecular diagnostic method with excellent analytical performance, though somewhat lower clinical performance, influenced by various preanalytical and method-specific factors. (IDSA, 2023; Teymouri et al., 2021). On May 5, 2023, when the WHO officially declared the end of the COVID-19 pandemic as a global public health emergency, Estonia had recorded 26,125 hospitalizations with COVID-19 (TEHIK, 2023) and 3,010 deaths (Health Board, 2023). The highest number of COVID-19 deaths occurred in 2021 (Lutsar & Emor, 2023), surpassing those from external causes, which are traditionally among the three most common causes of death in Estonia, after cardiovascular deaths and cancers (Estonian Institute for Health Development, n.d.-a). Deaths related to circulatory system diseases also peaked in 2021, coinciding with the surge in COVID-19 mortality (see Fig.1).

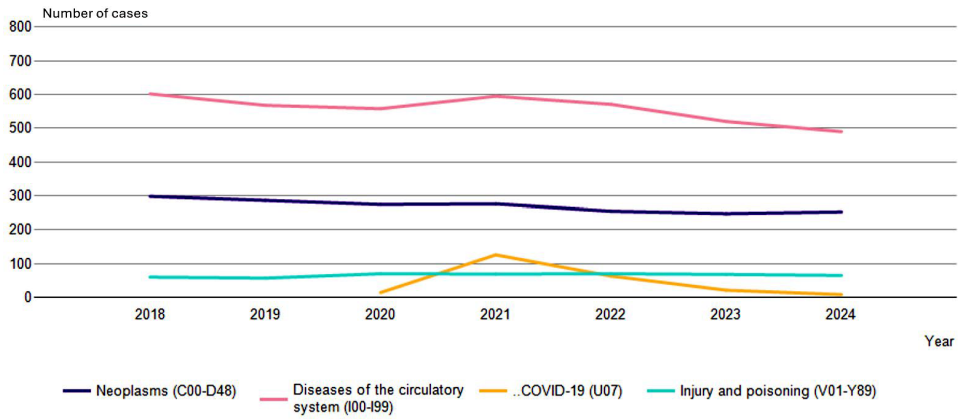

Figure 1. Leading Causes of Death in Estonia (2018 – 2024), mortality rates per 100,000 population (Source: Health Statistics database of the National Institute for Health Development)

COVID-19 vaccination in Estonia started on 27 December 2020, in alignment with the European Union's coordinated rollout (European Commission, n.d.). The initial approach prioritized healthcare workers, elderly individuals, and residents of long-term care facilities, then expanded to include individuals with specific diseases and conditions that put them in the COVID-19 risk group, based on the National Immunoprophylaxis Expert Committee's suggestions (Ministry of Social Affairs, 2021).

This targeted approach continued through the first quarter of 2021, ensuring early protection for the most vulnerable groups in the population. In May 2021, Estonia shifted to mass vaccination, opening access to all individuals over 16 years old regardless of risk category (Ministry of Social Affairs, 2021).

Estonia's COVID-19 vaccination program had several strengths, including a strong digital infrastructure (e.g., online booking and vaccination certificates), the use of mobile units and on-site vaccinations for disabled people, centralized government coordination with consistent public communication (e.g., interactive pandemic map), and the involvement of family physicians in direct informing and vaccination of at-risk groups. The program was also integrated with broader public health measures such as testing and contact tracing. However, it faced challenges, including slightly lower vaccine uptake compared to the EU average, as well as vaccine hesitancy and reduced coverage in specific groups and regions (e.g., Ida-Viru) (Palmer et al., 2021).

As of December 24, 2021, 839,193 individuals (63% of the population) had received at least one dose of a COVID-19 vaccine, and 811,218 individuals (61%) were fully vaccinated, with 75% coverage among the elderly population aged 60 and above (*Estonia: Vaccination against COVID-19 by Date 2023*, n.d.; Health Board, 2021). Following the rollout of Estonia's vaccination program, the vast majority of individuals hospitalized with COVID-19 were those unvaccinated (Health Board, 2022).

2.3 COVID-19 disease

2.3.1 Clinical features of COVID-19

COVID-19 presents a wide range of clinical features with potential to evolve from mild upper respiratory tract infection to acute respiratory failure, sepsis, and death, depending on the variant of the virus and individual-level host factors (D. Wang et al., 2020; F. Zhou et al., 2020), such as age, sex, and comorbidities. Huang and Chen et al. were among the first who independently described clinical and laboratory features of patients admitted to Wuhan hospital with later confirmed SARS-CoV-2 infection (Chen et al., 2020; Huang et al., 2020).

Early COVID-19 studies revealed that fever (78%), cough (57%), and fatigue (31%) were the most common patient-reported or clinician-observed symptoms in adults with laboratory-confirmed SARS-CoV-2 infection (Grant et al., 2020). The median times from initial symptoms to hospitalization and development of respiratory failure were 7 and 8 days, respectively (Kakodkar et al., 2020; Mehta et al., 2021). Up to one-third of patients hospitalized with COVID-19 required admission to the ICU due to hypoxemia, with the potential to develop acute respiratory distress syndrome (Chen et al., 2020; Huang et al., 2020; Moore & June, 2020). Among hospitalized patients, 88% exhibited abnormal lung findings on chest computer tomography (CT) scans, and 73% exhibited bilateral pneumonia (Fang et al., 2020). The observation of abnormal CT findings in patients with normal X-ray findings raised concerns about the reliability of imaging in COVID-19 diagnostics (Çinkooğlu et al., 2021). Imaging (X-ray or CT) was recommended by WHO even for mild cases to guide hospitalization decisions (WHO, 2020f), while several other guidelines, including those implemented in Estonia, suggested reserving CT for more severe, clinically indicated cases, due to its limited specificity and inability to rule out disease progression (American College of Radiology, 2020; Estonian Society of Family Doctors, 2022; Kuo et al., 2021; Simpson et al., 2020). Additionally, several cases of atypical presentation of underlying pneumonia (i.e. diarrhea or heart palpitations without fever or cough) caused a diagnostic challenge (An et al., 2021; K. Liu et al., 2020; Luo et al., 2021).

Abundant research conducted during the early years of the pandemic has highlighted the systemic nature of COVID-19, as it can present as a systemic inflammatory disease leading to severe outcomes, including multi-organ failure, excessive immunological response, and multiple thrombotic events (Davitt et al., 2022; Guo et al., 2020; Klok et al., 2020; Moore & June, 2020; Remy et al., 2021; Shankar et al., 2021; T. Wu et al., 2020).

Multiple theories have been proposed to explain the systemic involvement of COVID-19, including the ubiquitous distribution of ACE2 receptors throughout the human body, direct injury caused by viral entry, organ injury resulting from a cytokine storm, and various autoimmune processes that follow the acute phase of COVID-19 (Davitt et al., 2022; McMillan et al., 2021; Moore & June, 2020; Shirbhate et al., 2021). Cytopathic effects of human coronaviruses on airway

epithelial cells have been known previously. One of the downsides of this cytopathic effect is the formation of syncytia, i.e, fusion of SARS-CoV-2-infected cells with ACE2-presenting neighbouring cells and formation of a multinucleated mass of cytoplasm that lacks its functionality (Buchrieser et al., 2020). Transmembrane Serine Protease 2 (TMPRSS2), a host serine protease highly expressed in lungs, gastrointestinal tract, and kidneys, enhances viral entry and syncytia formation by suppressing innate immunity and promoting fusion with ACE2-expressing cells. Since androgens regulate TMPRSS2, its higher expression in men may contribute to sex-based differences in COVID-19 severity (Piva et al., 2021; The Human Protein Atlas, n.d.).

Although COVID-19 severity was initially attributed to hyperinflammation involving neutrophils and complement activation, emerging evidence suggests that immunosuppression, marked by lymphopenia and impaired macrophage function, may drive disease progression and vulnerability to secondary infections (Davitt et al., 2022).

On the other hand, typical for coronaviruses, a significant proportion of individuals infected with SARS-CoV-2 experienced no symptoms or exhibited clinical features of mild upper respiratory tract infections (i.e., common cold), which were too mild to warrant restrictions set for individuals with symptomatic COVID-19, contributing to its explosive dissemination (Ma et al., 2021; Shang et al., 2022).

Several systematic reviews have identified the most common symptoms and clinical manifestations of COVID-19, often categorized by affected organ systems, reflecting not only the specific symptomatology of the disease but also its associated complications (See Fig. 2) (Fu et al., 2020; Gupta et al., 2020; Hatmi, 2021; Knight et al., 2022; Legrand et al., 2021; Y. Li et al., 2024; Mehta et al., 2021).

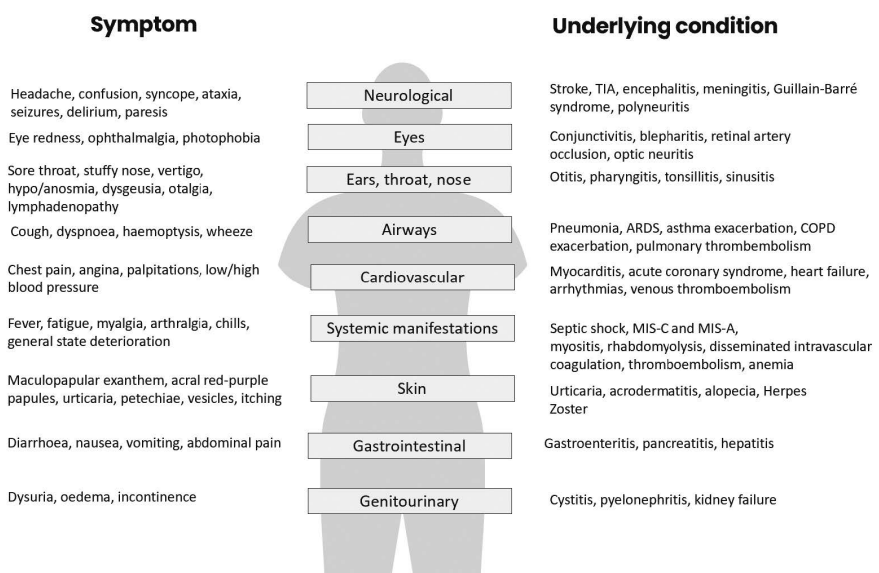

Figure 2. Patient-reported COVID-19 symptoms and corresponding diagnoses accompanying COVID-19.

The clinical picture and severity of COVID-19 have evolved with the emergence of new SARS-CoV variants, the acquisition of natural or vaccine-induced immunity by the vast majority of the population, and the increased availability of antiviral and immunomodulating therapies (Meyerowitz et al., 2024; Torabi et al., 2023). The Delta and Omicron variants had the highest and lowest proportions of severe cases (6.6% vs. 1.5%, respectively), based on risks of hospitalization, ICU admission, need for ventilation, and death (Arabi et al., 2023; Yuan et al., 2023).

2.3.2 Defining COVID-19 severity

Different health organizations and leading international health authorities have defined the severity stages of COVID-19 as mild, moderate, severe, and critical, based on clinical symptoms, oxygen saturation (SpO_2), respiratory rate, and the need for medical interventions. However, the criteria for defining the severity of COVID-19 cases vary somewhat across them (A. M. Cheng et al., 2023; IDSA, 2021; National Health Service, 2021; National Institute of Health, 2024; WHO, n.d.-a), with definitions often being arbitrary and extrapolated from non-COVID-19 critical care studies (Cajanding, 2021). Commonalities among definitions include the use of oxygen saturation (SpO_2) and respiratory rate as indicators of hypoxia. Mild cases usually maintain normal SpO_2 levels and lack pneumonia features, while moderate cases show signs of pneumonia and mild hypoxia (SpO_2 $\geq$ 90–94%). Severe cases exhibit significant hypoxia (SpO_2 < 90–93%) and clinical signs of tissue perfusion impairment or deterioration, often necessitating hospitalization. Critical cases involve respiratory failure, septic shock, or multi-organ dysfunction, requiring intensive care or mechanical ventilation. Differences among COVID-19 severity definitions lie in the specific thresholds and clinical markers used to define them. For example, WHO defines severe cases as SpO_2 < 90% on room air (WHO, n.d.-a), whereas the Infectious Diseases Society of America (IDSA) adopts a threshold of below 94% (IDSA, 2021). The National Institutes of Health (NIH/USA) and the National Health Service (NHS/UK) incorporate additional signs like confusion scores (e.g., NEWS2) and radiological features on lung X-rays (A. M. Cheng et al., 2023; National Institute of Health, 2024). Inconsistency in disease severity determinants across studies, variations in clinical thresholds, and healthcare system capacities may pose challenges to the comparability of research on severe COVID-19 risk factors, survival analyses, and the interpretation of therapeutic responses (Guérin et al., 2022). To systematize and standardize COVID-19 investigation, WHO and partner organizations defined three core outcome measures suggested for use in research: viral burden (quantitative PCR or cycle threshold), patient survival (hospital discharge or 60-day mortality), and the WHO Clinical Progression Scale, which tracks disease severity, symptom intensity, and resource use over time (Marshall et al., 2020).

In Estonia, symptoms linked to severe COVID-19, such as shortness of breath, severe chest pain, somnolence, hemoptysis, SpO2 on room air $\leq$ 92%, respiratory rate over 30/minute, bradycardia or tachycardia, and blood pressure below 90/60 mm Hg, was commonly used as indicators for hospitalization, closely aligning

with international definitions of severe and critical disease stages (Estonian Society of Family Doctors, 2022).

Asymptomatic SARS-CoV-2 infection – consistently defined across guidelines as a positive test result in individuals without any symptoms of COVID-19 at the time of testing – has been reported to account for up to 32% of cases. This definition covers both presymptomatic cases who develop symptoms as the infection progresses, and the ~20% who remain asymptomatic throughout the infection (CDC, 2024; National Institute of Health, 2024; WHO, n.d.-a).

2.4 Health-related consequences of COVID-19

Terminology related to the consequences of COVID-19 varies across studies and is continuously evolving (Gutzeit et al., 2025). Thus, COVID-19 can cause a wide range of effects, including symptoms that are not explained by other causes, as well as both symptomatic and asymptomatic underlying organ damage leading to a pathophysiological cascade that results in complications across multiple organ systems.

The WHO defines long COVID as *a range of symptoms* that persist or emerge three months after infection and last at least two months, and are unexplained by an alternative diagnosis (WHO, 2022). It affects about 10–30% of SARS-CoV-2-infected individuals, with lower rates reported in healthcare record studies compared to self-reports (Woodrow et al., 2023). Estonian data align with these findings, showing that 22% of COVID-19 patients reported symptoms consistent with long COVID-19 and reduced quality of life six months post-infection (Uusküla A et al., 2022).

Apart from symptomatic cases, some studies show that over 50% of COVID-19 survivors may have organ damage without accompanying symptoms, highlighting that post-COVID conditions can involve serious pathophysiological effects beyond visible illness or *syndrome* (Woodrow et al., 2023). Variations across studies on post-COVID-19 sequelae may be attributed to differences in design, inconsistent terminology, and the methods used to address biases such as recall and selection bias (Rochmawati et al., 2024; Dirican & Bal, 2022). Because different post-COVID-19-related terms are often used interchangeably, the relationship between self-reported symptoms and underlying organ damage remains poorly understood. Variations in the acknowledgement, recognition, and management of COVID-19 sequelae across countries make it difficult to assess the actual burden of *long COVID* accurately. Specialized long COVID clinics have been established across many European countries to deliver the interdisciplinary care required to address the multifaceted sequelae of COVID-19 (Gonzales Esponosa & Suzuki, 2024). In Estonia, a national guideline for the diagnosis and management of patients with long COVID in primary care has been issued (Rospu et al., 2022). However, its implementation has not been systematically evaluated.

One of the central hypotheses of *long COVID* is the persistence of SARS-CoV-2 infection and continuous stimulation of the immune system, which contributes to chronic inflammation and the breakdown of healthy cells and tissues, as viral proteins and RNA have been found in various tissues long after acute infection (Ceulemans et al., 2021; Cheung et al., 2022; H. E. Davis et al., 2023; Tejerina et al., 2022). Immune and hormonal dysregulation are other major contributors, marked by elevated pro-inflammatory cytokines (e.g., IL-6, TNF-α, IL-3), T cell exhaustion, reduced naive T cells, persistent activation of B cells, and low cortisol in individuals with long COVID, resembling patterns seen in chronic fatigue syndrome after other viruses and in cases of autoimmune diseases (J. Klein et al., 2022; Podolska et al., 2024; Renner et al., 2025). Markers of endothelial dysfunction and reactivation of cytomegalovirus or Epstein-Barr virus have been reported in long COVID haulers (Cervia-Hasler et al., 2024). Alterations in biochemical markers indicate that the immune system is skewed toward a chronic inflammatory state in individuals with long COVID, impairing its ability to respond to new threats (incl. new infections) and causing subtle, ongoing internal damage (Renner et al., 2025). Studies consistently report that older age, female sex, SARS-CoV-2 strain, COVID-19 severity, multiple chronic conditions (especially cardiometabolic and renal), poor mental health, sociodemographic disparities, vaccination status, and reinfections significantly raise the risk of long COVID (Bowe et al., 2022; Hedberg et al., 2023, 2023; Pietzner et al., 2024; Shabnam et al., 2023; Thompson et al., 2021).

It's worth noting that SARS-CoV-2 is not the only virus capable of causing long-term health effects, as long COVID shares clinical and immunological features with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), which can be triggered by other viruses. Past pandemics, such as the 1889 and 1918 influenza outbreaks, left a subset of survivors with persistent symptoms, including fatigue, neuralgia, hypersomnolence, and reports of sudden deaths following infection (Hoffman & Vilensky, 2017). Both SARS-CoV-2 and other respiratory infections have been linked to a reduced quality of life and lasting symptoms, including sleep disorders, palpitations, and dyspnea, highlighting shared long-term impacts across pathogens (Vivaldi et al., 2023). Therefore, both ME/CFS and long COVID are real, biologically based illnesses with overlapping pathophysiology and potential to evolve to organ damage and complications related to it (Komaroff & Lipkin, 2023).

Recognizing and managing COVID-19 sequelae poses a significant challenge, especially in primary care, where clinicians must navigate substantial uncertainty related to nonspecific symptoms while remaining alert to subtle signs of organ damage. Given these findings – and the fact that many severe health conditions, such as heart failure or ischemic disease, often remain asymptomatic until the advanced stage of disease – there is growing support for expanding the definition of post-COVID-19 sequelae to include silent organ damage, even in the absence of overt symptoms (Ewing et al., 2024).

2.5 Cardiovascular sequelae of COVID-19

Among the most dangerous and potentially debilitating consequences of COVID-19 are those affecting the cardiovascular system, such as infection-driven myocarditis, pericarditis, arrhythmias, heart failure, and thromboembolic events (Hatmi & Mahboobian, 2025). Myocarditis during the acute phase of COVID-19 in hospitalized patients was related to increased mortality (M. G. Davis et al., 2022). Another study performed in the early stage of the pandemic found cardiac MRI abnormalities in 78% of COVID-19 patients 71 days after SARS-CoV-2 infection, regardless of initial disease severity (Puntmann et al., 2020). Moreover, COVID-19 tripled the risk of impaired myocardial flow reserve, indicating microvascular damage, which peaks at 6–9 months post-infection, with greater risk in severe COVID-19 cases (A. I. Ahmed et al., 2023). Endothelial dysfunction has been proposed as a key mechanism in post-COVID cardiovascular complications, driven by viral invasion via ACE2, persistent viremia, and chronic inflammation, leading to impaired vasodilation, increased vascular permeability, thrombogenesis, microvascular injury, ischemia, or heart failure (Aljadah et al., 2024). Additionally, studies suggest that autoimmune responses may also play a role in cardiomyocyte damage, leading to abnormalities on imaging or functional tests (Cremonesi et al., 2023; Fagyas et al., 2022).

Cohort studies have revealed an increased incidence of cardiac diseases following COVID-19. A U.S. Veterans Affairs study reported a 63% higher risk of any cardiovascular disease, 72% for heart failure, and 52% for stroke within a year of infection, with greater severity of COVID-19 linked to higher risk. The excess burden per 1,000 persons included 45.3 additional cases of any cardiovascular disease, 11.6 cases of heart failure, 7.3 cases of ischemic heart disease, and 5.5 extra cases of cerebrovascular disorders (TIA and stroke) (Xie et al., 2022). The risk of severe cardiovascular complications was higher during the early pandemic, driven by ancestral SARS-CoV-2 variants. In contrast, studies from the Omicron era report fewer cardiovascular and long-COVID complications, likely due to milder infections and widespread vaccination (Antonelli, Pujol, et al., 2022; Okamoto et al., n.d.; Wan et al., 2023 Wee et al., 2024). However, the findings of studies conducted during the Omicron and post-Omicron periods may be biased due to the end of mandatory testing and potential underreporting of mild COVID-19 cases, which could limit research opportunities on cardiovascular outcomes in this subgroup.

It remains unclear whether the damage caused by the virus and the increased risk of cardiovascular complications are temporary or long-lasting, and how these factors relate to sex, age, disease severity, and vaccination status. Clarifying this could improve our ability to estimate the actual burden of the disease and better understand long-term post-infectious sequelae.

2.6 Risk factors for severe COVID-19

Systematic reviews and meta-analyses have identified a broad spectrum of factors associated with increased risk of severe COVID-19 outcomes. These factors can be broadly categorized into intrinsic and extrinsic parameters, which are interrelated and together form the broader framework of health determinants. (Arah, 2009) Intrinsic factors refer to individual-level characteristics or personal choices, including demographic attributes (e.g., age, sex), health status (e.g., comorbidities), immunological and genetic predispositions, and behavioral traits such as help-seeking behavior or occupational and social exposure patterns that are shaped by personal choices or circumstances. Extrinsic factors, on the other hand, encompass population-level or contextual determinants. These may include the circulating viral strain, transmission level, governmental virus containment strategies, regional testing policies, or healthcare capacity during different stages of the pandemic, which shape the observed virulence and evolving severity of COVID-19. (Perez-Guzman et al., 2023)

Advanced age has emerged as the most consistent and powerful predictor of severe COVID-19 (Du et al., 2021; Xia et al., 2024; F. Zhou et al., 2020). This association is thought to be attributed to immunosenescence, which increases vulnerability to infections, impairs pathogen clearance, and weakens vaccine responses. Additionally, a chronic inflammation state arising from the accumulation of comorbidities and low-grade inflammation associated with aging, primes the immune system for exaggerated reactions, such as cytokine storms observed in severe COVID-19 cases (Tizazu et al., 2022).

Sex-related differences in COVID-19 severity have been consistently observed across multiple studies, highlighting male sex as a significant risk factor for adverse COVID-19 outcomes. A systematic review and meta-analysis of 31 studies found that males represented a disproportionately higher proportion of critical COVID-19 cases (71%) and COVID-19-related deaths (69%). These findings were consistent across both Asian and Western populations, suggesting that biological rather than cultural factors may underlie this disparity (Galbadage et al., 2020). Kelada et al. (2020) identified sex-based differences in immune responses, hormone regulation, and ACE2 expression, noting that males typically have lower IgG levels, fewer T-helper cells, and higher levels of proinflammatory cytokines (IL-6 and TNF-α), factors linked to greater COVID-19 severity (Kelada et al., n.d.). A meta-analysis of 77 studies further supported these findings, as higher levels of specific immune signaling molecules in males were linked to greater severity and mortality (Hu et al., 2022). Moreover, autoantibodies against type I interferons – the key first-line defense against severe COVID-19 – were found more frequently in males than in females (Bastard et al., 2020). Genetic variations in ACE2 expression genes may also explain observed sex-based differences in clinical outcomes. Because the ACE2 gene is located on the X chromosome, males – having only one copy – may be more vulnerable to ACE2 deficiency caused by SARS-CoV-2 invasion (Keikha & Karbalaei, 2022).

Metabolic disorders play a central role in the progression of COVID-19. Obesity and non-alcoholic fatty liver disease have been identified as independent risk factors for severe COVID-19 course and mortality (Haber et al., 2024; Kurniawan & Hariyanto, 2023; Nagarajan et al., 2022; Tadayon Najafabadi et al., 2023).

Hyperglycemia exacerbates inflammatory responses and compromises immune function (Kaminska et al., 2021; Kastora et al., 2022). Thus, prediabetes has emerged as an underestimated but important risk factor for severe outcomes in COVID-19 (Heidarpour et al., 2021). On the other hand, a systematic review by Schlezinger et al. revealed that poor outcomes are more closely linked to advanced diabetes and overall health status than to diabetes alone (Schlesinger et al., 2023). An umbrella review of 84 studies from early in the pandemic found that cerebrovascular and cardiovascular diseases significantly increased the risk of ICU admission and death from COVID-19 (Harrison et al., 2021; Lee et al., 2021). While hypertension and dyslipidemia were frequently associated with poor outcomes, particularly when coexisting with other metabolic conditions (Hariyanto & Kurniawan, 2020; C. Li et al., 2023), more advanced presentation of cardiac disease, such as heart failure, exhibited even greater association (CAPACITY-COVID Collaborative Consortium and LEOSS Study Group, 2022). Chronic kidney disease (CKD) has shown the strongest association with increased mortality and severity of COVID-19, as reported in numerous cohort studies and the systematic reviews based on them. Additionally, COVID-19 itself is believed to raise the risk of kidney injury among survivors, highlighting a bidirectional relationship between these conditions (Harrison et al., 2021; Lee et al., 2021; Sabaghian et al., 2022). Chronic obstructive pulmonary disease has also been associated with poor outcomes (Gerayeli et al., 2021). However, the evidence regarding asthma remains mixed, with some studies suggesting no significant increase in COVID-19 severity (Soeroto et al., 2021; T. Wu et al., 2022).

Apart from age, sex, and comorbidities, a range of genetic factors have been explored in relation to COVID-19 severity, as they may influence COVID-19 severity by affecting RAAS pathway molecules, thereby shaping outcomes in RAAS-related conditions, including COVID-19. Keikha et al. (2022) found that ACE1 and ACE2 gene variants were linked to severe COVID-19 risk, with the ACE1 DD genotype tripling risk and the II genotype reducing it by 40% (Keikha & Karbalaei, 2022). Some studies also suggest ABO blood group O offers protection against infection and severe outcomes (N. Liu et al., 2021; Mortensen et al., 2023).

Lifestyle and environmental factors also play a significant role. Thus, smoking has been consistently associated with increased severity and mortality, especially among younger adults (Kumar et al., 2021; Patanavanich & Glantz, 2021). Racial or ethnic minority, residency in rural areas, and lower socioeconomic status, incl. lower education level, posed higher risks of infection, hospitalization, and COVID-19-related death (Anzalone, Horswell, et al., 2023; Khanijahani et al., 2021).

In addition to these individual-level risk factors, each new VOC of SARS-CoV-2 exhibited distinct biological characteristics that affected the transmission

rate and intrinsic severity of the pathogen, with Alpha and Delta commonly showing the highest CFR (Perez-Guzman et al., 2023; Yuan et al., 2023).

The integration of demographic and clinical risk factors for severe COVID-19 was incorporated into the development of vaccination strategies in many countries, with the WHO among the first to issue formal advice on vaccine development, distribution, and risk group vaccination against COVID-19 in mid-2020 (WHO, 2020a, 2020d).

2.7 The role of vaccination in mitigating SARS-CoV-2 infections and severe COVID-19

The COVID-19 pandemic accelerated the adoption of next-generation vaccine platforms, including viral vector vaccines (AstraZeneca's ChAdOx1 and Janssen's Ad26.COV2.S, an adenoviral vector vaccine) and mRNA technologies (Pfizer-BioNTech's BNT162b2 and Moderna's mRNA-13273 vaccines). Their rapid development was enabled by decades of research on mRNA platforms for MERS and Zika, adaptive trial designs from the Ebola outbreak, regulatory innovations from the HIV pandemic (e.g., Emergency Use Authorization), and mRNA delivery systems from cancer research (Saag, 2022).

A key breakthrough in COVID-19 vaccine development was the use of lipid nanoparticles (LNPs), initially designed for gene therapy, to stabilize and deliver mRNA into cells. mRNA vaccines being in use encode the full-length SARS-CoV-2 spike protein, enabling a broader immune response than vaccine candidates targeting only RBD (Bettini & Locci, 2021; Gote et al., 2023).

Starting in December 2020, after BioNTech developed the first mRNA-based COVID-19 vaccine, the WHO granted EUA status to several dozen vaccines by the end of 2023, with more than a hundred vaccine candidates still under research. (Ao et al., 2023) To date, most of the EUA-granted COVID-19 vaccines have achieved prequalification status, ensuring that they meet WHO standards for vaccine quality, safety, and efficacy, are suitable for the target population, and are compatible with appropriate concomitant products (WHO, 2025).

A large meta-analysis of 33 vaccine effectiveness (VE) studies from Europe, covering over 56 million people, confirmed that COVID-19 vaccines are both effective and safe, with mRNA and viral vector vaccines capable of inducing both antibody and T cell responses, which are essential for long-term protection. The primary series of vaccination showed 70.7% overall effectiveness, higher against pre-Omicron variants (77%) than against Omicron (26%), with protection waning over time to 53% at six months. Boosters significantly improved protection, especially against severe outcomes like hospitalization and death: 95% (pre-Omicron) and 83% (Omicron), with only slight declines after three months (G. Zhou et al., 2025).

Despite the vaccines' exceptional efficacy against severe disease, hospitalization, and death in the initial stages of the pandemic, the further effectiveness of COVID-19 vaccines has been challenged by frequent mutations in the SARS-

CoV-2 spike protein, which facilitates immune escape, and by the natural waning of vaccine-induced immunity over time. As a result, breakthrough infections have become increasingly common. A study of individuals over 60 years old from 11 countries found that VE against symptomatic COVID-19 was approximately 30%, depending on their previous vaccination history, and declined significantly over three months during the prevalence of the highly contagious Omicron XBB variant (Laniece Delaunay et al., 2024). Link-Gelles et al. found that the 2023–2024 monovalent XBB.1.5 COVID-19 vaccines provided 24% protection against emergency visits and 48% against critical illness, with the highest protection observed at two months, declining to 16% for critical illness by six months. Effectiveness was higher during the XBB period than during the JN.1 period, and a second booster in adults aged 65 years and older provided modest added protection (21% for ED visits, 18% for hospitalization) (Link-Gelles et al., 2025).

Despite declining effectiveness against emerging variants of SARS-CoV-2, COVID-19 vaccine boosters demonstrated protection against severe COVID-19 and death. A large-scale study conducted within the U.S. Department of Veterans Affairs health care system assessed the effectiveness of mRNA COVID-19 booster vaccines during the Omicron variant era. Involving nearly one million participants, the study found that booster doses of BNT162b2 and mRNA-1273 vaccines significantly reduced the risks of hospitalization and death, with a VE of 53% against hospitalization, and 79% against death within four months post-booster. These benefits were consistent across vaccine types and age groups, with even greater protection observed in individuals with higher comorbidity burden and those who received their primary vaccination more than nine months before (Ioannou et al., 2022).

Some studies suggest that heterologous prime–boost vaccination strategies (i.e., a combination of an mRNA vaccine with a viral vector vaccine) may offer superior protection and higher neutralizing antibody titers compared to a homologous regimen. This might be particularly important in the context of emerging variants and vaccine supply challenges (Deming & Lyke, 2021).

However, concerns have been raised regarding the estimation of VE in COVID-19 studies, suggesting that they may be somewhat biased due to various methodological and contextual factors. Thus, vaccine *efficacy* demonstrated in randomized clinical trials may not align with the vaccine *effectiveness* observed in real-world settings. Overestimation occurs in settings where vaccinated individuals primarily interact with other vaccinated individuals, such as during lockdowns or in highly vaccinated communities, because their risk of acquiring breakthrough infection in that case is naturally decreased. Conversely, underestimation often occurs in household studies where vaccinated individuals – such as parents – frequently interact with unvaccinated household members – typically children – thereby increasing their own exposure risk while also indirectly protecting the unvaccinated from infection. These biases are compounded by factors such as waning immunity, variant-specific immune escape, differences in study design, and unmeasured social mixing patterns that shape exposure risk (i.e, how

frequently vaccinated individuals interact with unvaccinated individuals) (De-Leon & Aran, 2025).

Additionally, individuals' vaccination status may influence their self-testing behavior, and the results of self-tests may, in turn, affect consultation decisions, potentially biasing the results of observational studies conducted in primary healthcare during the vaccination era that employ self-testing data (Lanièce Delaunay et al., 2025). That may be the case in studies estimating VE against symptomatic SARS-CoV-2 infection without progressing to severe disease forms, where data reliability is not ensured by robustness of the outcome (i.e, hospitalization).

Despite their effectiveness, vaccines have been associated with rare severe adverse events. A higher risk of myocarditis was estimated after vaccination with the mRNA vaccine in the safety analysis. However, the infection itself posed a several times greater risk, with a four times higher risk of myocardial infarction after SARS-CoV-2 infection, with no additional risk after vaccination (Barda et al., 2021). A meta-analysis of 42 cohort studies providing real-world data on vaccine safety reported that COVID-19 vaccination had no link to acute cardiovascular events, including myocardial infarction (Chang et al., 2023). Buchan et al. reported 297 cases of myocarditis (0.002%) among 19.7 million vaccinated people, with higher rates in young males and those receiving mRNA-1273 (Buchan et al., 2022). Karlstad et al. found 1149 cases (0.005%) among 23 million residents of Nordic countries, with increased risk after the second dose and mRNA-1273 vaccine (Karlstad et al., 2022). A cohort study of 46 million adults in the UK found a small increased risk of intracranial venous thrombosis and thrombocytopenia within 28 days of ChAdOx1-S vaccination in adults under 70. However, the absolute risk was very low, ranging from 0.9 to 3 cases of thrombotic events per million vaccinated individuals. BNT162b2 showed no such risks. In adults over 70 years, both vaccines were linked to reduced rates of arterial and venous thrombotic events compared to unvaccinated individuals (Whiteley et al., 2022). The negligible occurrence of myocardial infarction related to COVID-19 vaccination was further examined in a systematic review and meta-analysis, and no connection was found between them (Sadatnaseri et al., 2024). Despite these risks, the absolute incidence remains low, and vaccination is estimated to have saved over 14 million lives (Banerjee et al., n.d.).

2.8 The role of vaccination in preventing post-acute COVID-19 sequelae, focusing on cardiovascular outcomes

Vaccination stands out as the most extensively studied and widely implemented approach, offering significant protection against infection-related inflammatory responses. Its relevance is further amplified in the context of rising antimicrobial resistance, where preventing infections becomes increasingly critical. In 2025, the European Society of Cardiology (ESC) identified vaccination as a foundational pillar of primary cardiovascular prevention, as vaccination against infec-

tious diseases has shown promising results in reducing cardiovascular and overall mortality (Heidecker et al., 2025).

A cohort study of 46 million adults in the UK found that during the Delta SARS-CoV-2 wave, unvaccinated SARS-CoV-2-infected individuals had a much higher risk of arterial thrombotic events (718 additional events per 100,000; aHR 10.5) compared to vaccinated individuals (229 additional events per 100,000; aHR 2.1). Hospitalized patients had the highest risk (aHR 19.6), which was reduced with vaccination (aHR 7.4). The highest risk occurred within four weeks of infection and persisted for up to two years in the unvaccinated. (Cezard et al., 2024) In a cohort of over 1.9 million COVID-19 patients, vaccination was associated with a 41% reduced risk of MACE post-infection. MACE occurred in 0.5% of fully vaccinated and 0.7% of unvaccinated individuals during the six-month follow-up period. (Jiang et al., 2023) Vaccination with mRNA vaccines was associated with a significantly lower risk of myocardial infarction and stroke within 28 days after SARS-CoV-2 infection in patients with preexisting cardiovascular disease, with greater protection observed after second and third booster doses (51%, 70%, and 83% lower risk, respectively) (Ye et al., 2023). In a large Korean cohort study encompassing data of 231,037 patients, full COVID-19 vaccination was associated with a 58% reduction in the risk of acute myocardial infarction and ischemic stroke 31–120 days following SARS-CoV-2 infection. Subgroup analyses showed consistent risk reduction across age, sex, and comorbidity categories, with the most pronounced benefit observed in older adults (≥65 years), those with hypertension, dyslipidemia, no previous history of outcome event, and non-severe COVID-19 cases (Kim et al., 2022). In patients with COVID-19–related acute kidney injury, being unvaccinated before hospitalization was linked to a five-fold increase in in-hospital mortality and a four-to five-fold rise in long-term mortality compared to those fully vaccinated (Nobakht et al., 2025).

The protective effects of vaccination against cardiovascular complications following infection are not unique to COVID-19 vaccines; similar benefits have been observed with vaccines targeting influenza, *Streptococcus pneumoniae*, respiratory syncytial virus (RSV), pertussis, and herpes zoster (Rademacher et al., 2024), with lower all-cause mortality and serious cardiovascular events in individuals with pre-existing high-risk conditions (X. Liu et al., 2025; Shih et al., 2025). Vaccination not only reduces the severity of infections but also disrupts inflammatory pathways associated with cardiovascular complications. These findings underscore a broader immunological principle: infections can act as potent triggers of systemic inflammation, which plays a central role in the pathogenesis of atherosclerosis. Inflammatory processes influence plaque formation, progression, and rupture. Growing evidence suggests that both viral and bacterial pathogens contribute to this cascade by activating the innate immune pathway, leading to the release of pro-inflammatory cytokines and the destabilization of pre-existing atherosclerotic plaques (Dickson & Gotlieb, 2003; Halvorsen et al., 2008; Kong et al., 2022). Therefore, targeting these inflammatory pathways could

be a promising therapeutic intervention beyond traditional lipid-lowering strategies (Kong et al., 2022).

The protective effects of COVID-19 vaccination against post-acute sequelae, including cardiovascular complications, are insufficiently understood due to the time-dependent nature of these outcomes. It remains unclear whether the observed benefits in reducing post-COVID complications are primarily due to the vaccine's ability to attenuate the severity of the acute phase of infection, or whether its protective effects extend beyond the immediate course of illness, and whether these effects are consistent across different demographic and clinical subgroups.

2.9 Summary of literature review

The COVID-19 disease, caused by the novel coronavirus SARS-CoV-2, emerged in late 2019 and rapidly escalated into a global health crisis, overwhelmed healthcare systems and caused profound disruptions across economic, healthcare, and societal levels due to its high transmissibility, diverse clinical manifestations, and absence of pre-existing immunity in the population during the early stages of the pandemic.

The Initial public health efforts focused on controlling transmission and reducing mortality (the "flattening the curve" strategy). However, it quickly became clear that COVID-19 is far more than an acute illness – it is a systemic disease with profound impacts extending far beyond the acute phase of infection. The observed shift in SARS-CoV-2 pathogenicity through the COVID-19 pandemic – from a virus causing high rates of severe illness to one associated with predominantly mild or asymptomatic infections – demonstrates that virulence is not a fixed trait, but a dynamic and context-dependent concept shaped by both host and viral factors.

Comparing mortality rates without proper contextual adjustments may be unreliable due to biases arising from differences in testing practices, reporting standards, healthcare settings, viral variants, healthcare capacity, socioeconomic conditions, and data quality, all of which often vary significantly between countries. Most early COVID-19 research relied on data from symptomatic patients, seroepidemiological studies, or selective samples of severely ill COVID-19 patients. These approaches lack generalizability, limiting insights into infection risk and the broader impact of COVID-19. Understanding both the risk of acquiring SARS-CoV-2 infection and the likelihood of severe disease is essential for effective prevention and guiding personalized public health strategies. Real-world population-based studies utilizing comprehensive, large-scale electronic health data with broad testing coverage and minimal selection bias toward severe cases can help mitigate the limitations inherent in hospital-centered studies. Understanding individual-level factors that influence disease severity, along with systematic, data-supported quantification of the strength of association between predefined risk factors in vaccinated and unvaccinated individuals, is an essential

component of after-action analysis. This research focused on evaluating the impact of established clinical and demographic characteristics, thereby contributing to evidence-based preparedness and response strategies.

Considering the evolving nature of immunity driven by host, viral, and external factors, such as vaccination, social frailty, or treatment compliance, it is essential to identify vulnerable populations within the shifting landscape of COVID-19-related threats. Research on post-acute COVID-19 sequelae has identified a broad spectrum of persistent symptoms and organ dysfunction following SARS-CoV-2 infection – often involving the cardiovascular system – which poses significant diagnostic and therapeutic challenges, particularly in the absence of specific, precise, and accessible diagnostic tools for this highly unspecific condition. COVID-19 sequelae are thought to result from a combination of direct viral invasion via ACE2 receptors, immune dysregulation, endothelial dysfunction, and persistent inflammation. Vaccination has proven highly effective in reducing the severity of acute COVID-19 and associated mortality. Emerging evidence also suggests that vaccines may mitigate the risk of long-term post-viral complications by attenuating the severity of the initial infection and modulating inflammatory responses. However, the durability of this protection, its relation to mortality, and consistency across different demographic and clinical subgroups need further investigation.

3. AIMS OF THE STUDY

This study aims to advance understanding of how individual-level factors influence susceptibility to SARS-CoV-2 infection, severity of COVID-19, and long-term health consequences, with particular attention to differences between vaccinated and unvaccinated populations. By generating evidence across these dimensions, the study seeks to inform more effective prevention strategies, risk stratification models, and post-infection management.

1. To identify individual-level risk factors for SARS-CoV-2 infection in both vaccinated and unvaccinated populations. Studies I–II
2. To investigate individual-level risk factors for severe COVID-19 among unvaccinated individuals with primary infection and vaccinated individuals with breakthrough infection. Studies I–II
3. To evaluate the long-term impact of pre-infection COVID-19 vaccination on major acute cardiovascular events and mortality following primary SARS-CoV-2 infection. Study III

4. MATERIALS AND METHODS

4.1 Study design

These studies form a cohesive body of research that leverages the same data infrastructure to examine COVID-19 risk factors and health sequelae among the general population, with a particular focus on the role and impact of vaccination on mortality and acute cardiovascular events.

All three studies utilize a retrospective cohort design. Study III extends the analysis by applying a TTE framework to enhance causal inference. Table 1 summarizes the methodological design, data sources, analytical frameworks, and primary objectives of the three studies that form the foundation of this dissertation.

Table 1. Core elements of the studies included in the dissertation.

Manuscript	Study I	Study II	Study III
Design	Retrospective cohort design with nested case-control analysis	Retrospective cohort study	Retrospective cohort study structured as a target trial emulation
Study period	February 26, 2020, to February 28, 2021	January 19, 2021, to February 9, 2022	April 2021 to March 2023
Aims	1. To identify risk factors for primary SARS-CoV-2 infection in the unvaccinated population.	1. To identify risk factors for SARS-CoV-2 BTI	To evaluate the long-term impact of pre-infection COVID-19 vaccination on MACE and mortality following primary SARS-CoV-2 infection.
	2. To identify risk factors of severe COVID-19 in the unvaccinated population.	2. To identify risk factors of severe breakthrough COVID-19	
Study groups	1. Individuals with SARS-CoV-2 infection vs. individuals without SARS-CoV-2 infection	1. Vaccinated individuals with primary BTI vs. vaccinated individuals who remained uninfected.	Unvaccinated individuals with primary SARS-CoV-2 infection vs vaccinated individuals with breakthrough COVID-19
	2. Individuals with severe COVID-19 vs. individuals with non-severe COVID-19	2. Vaccinated individuals with severe BTI vs vaccinated individuals with non-severe BTI	
Population and sample sizes	66,295 SARS-CoV-2 positive individuals; 254,958 randomly selected controls (matched 1:4)	184,132 SARS-CoV-2 infection-naive individuals who received at least a primary series of COVID-19 vaccination	18,223 vaccinated individuals; 15,331 unvaccinated individuals
Study period	26.02.2020 – 28.02.2021	19.01.2021 – 9.02.2022	1.04.2021 – 03.2023
Outcomes	Primary SARS-coV-2 infection Severe primary COVID-19	Primary BTI Severe primary BTI	MACE All-cause death
Covariables	Age, sex, CCI, CCI components, selected comorbidities, influenza, vaccination against influenza	Age, sex, education, CCI, selected comorbidities, hospital stay history, booster dose, and predicted testing propensity.	Age, sex, education, selected comorbidities

Manuscript	Study I	Study II	Study III
Statistical analysis	1. IR per 10,000 person-months for SARS-CoV-2 infection 2. Conditional logistic regression analysis to evaluate risk factors for SARS-CoV-2 infection (aOR, 95%CI) 3. Multinomial logistic regression model to evaluate risk factors for severe COVID-19 (aRRR, 95%CI)	1. IR per 10,000 person-days for breakthrough SARS-CoV-2 infection and severe COVID-19 2. Cox regression analysis to evaluate risk factors for BTI and severe BTI (aHR, 95%CI)	1. IR per 100 person-years for MACE and all-cause death 2. wIR and wIRR with IPT weights, utilizing Poisson regression with unequally spaced split timescales and penalized splines to assess the time-dependent nature of MACE and all-cause death after primary SARS-CoV-2 infection

4.2 Data sources

All three studies utilized the same core data sources within Estonia's national health system. This includes data from:

a) The Estonian Health Board (EHB): data on SARS-CoV-2 testing/results.

The EHB oversees communicable disease surveillance, epidemiological monitoring, and vaccination programs. (Habicht et al., 2018) (Health Board, n.d.) It collects and analyzes communicable disease notification data, including all SARS-CoV-2 cases via PCR or rapid antigen tests (WHO, 2020g).

b) Health and Welfare Information Systems Centre (TEHIK): data on COVID-19 vaccination, including vaccination dates and manufacturer for each vaccination episode.

The TEHIK manages electronic health records (EHRs) inserted in the Health Information System (HIS) and collects data on all interactions with healthcare providers, including medical care, laboratory test results, referrals, and vaccination information. According to the law, healthcare providers and laboratories in Estonia are obliged to report to the TEHIK, with an expected 100% coverage (TEHIK, n.d.-a) (TEHIK, n.d.-b).

c) the Estonian Health Insurance Fund (EHIF): data about participants' COVID-19 severity, comorbidities, and healthcare utilization.

Data about participants' COVID-19 severity, comorbidities and healthcare utilization were obtained from EHIF. By 2020, 95.2% of Estonia's population (1,328,889 people) was covered by public health insurance. Since the early 2000s, EHIF has maintained a comprehensive electronic database of healthcare services, including personal details, service utilization, diagnoses, procedures, and dates of care and death (EHIF, n.d.). The database includes diagnostic codes based on the International Classification of Diseases, tenth revision (ICD-10) (Ministry of Social Affairs, n.d.), and specific medical service codes: NOMESCO (Nordic Health and Welfare Statistics, 2021), EHIF-specific procedure codes (Riigi Teataja, n.d.).

d) the Causes of Death Registry: data on the death date.

The Causes of Death Registry collects data on all deaths registered in Estonia, as well as on deaths of Estonian residents who have died outside Estonia. Deaths are reported to the registry using a standardized death certificate, including the date of death, personal data of the deceased, causes and circumstances of death, and

sociodemographic data of the deceased (National Institute for Health Development, n.d.-a).

e) The Population Register: data on study subjects' education, native language, and ethnicity.

The population register is a database that consolidates key personal information about Estonian citizens, EU citizens registered in Estonia, and non-citizens with residence permits or rights to reside in Estonia. It is managed and updated by the Ministry of the Interior (Ministry Of The Interior, n.d.).

The unique personal identification code assigned to all Estonian residents (at birth or immigration) was used to link data between health databases (Enterprise Estonia, 2020).

The picture below depicts the periods during which study participants were involved, providing contextual alignment between public health developments and data collection. (TEHIK, 2023)

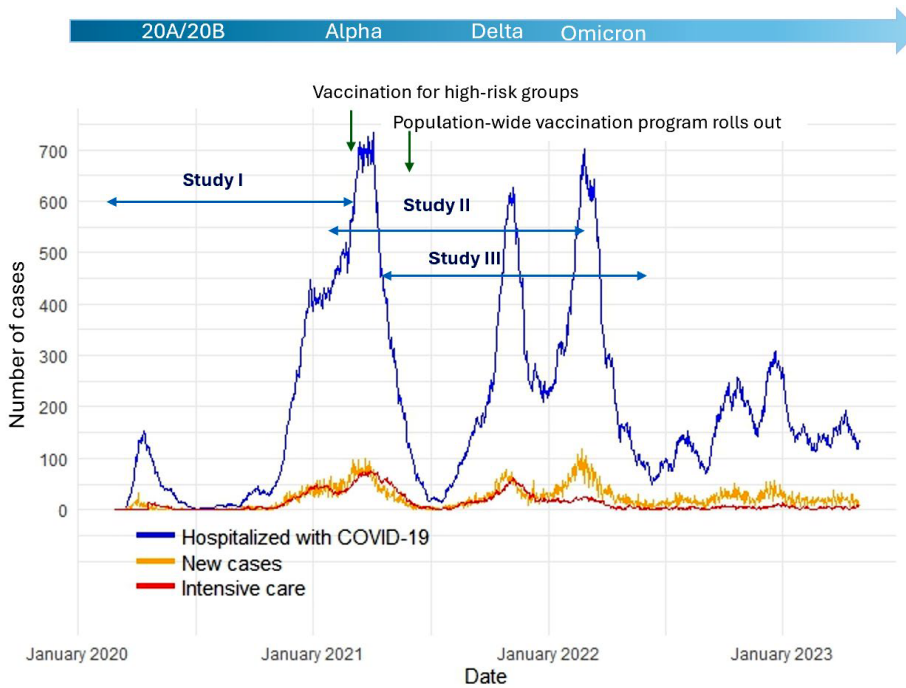

Figure 3. Daily number of individuals hospitalized with COVID-19, including intensive care cases and newly registered hospitalizations in Estonia, January 2020 – May 2023.

The graph also shows the timeframes for three separate research studies, labeled as Study I, Study II, and Study III. Additionally, the progression of different

SARS-CoV-2 variants – 20A/20B, Alpha, Delta, and Omicron – is marked along the timeline. The figure highlights key milestones in the vaccination effort, including the start of the risk group vaccination program and the subsequent population-wide vaccination rollout. (Source: The Estonian Health Board (assessed 01.06.2023)

4.3 Definitions in the studies

Definitions in Study I

COVID-19 cases were identified based on the collection date (index date) of the first positive SARS-CoV-2 specimen obtained from the EHB database. We included all confirmed COVID-19 cases for the period 26 February 2020 to 28 February 2021 in Estonia.

The control group consisted of a randomly selected subset of individuals insured by the EHIF. These individuals were alive on the COVID-19 case index date and showed no evidence of a positive SARS-CoV-19 PCR test. The case-to-control ratio was 1:4 (see Table 1)

Different levels of COVID-19 severity were assessed as *the outcome of interest*. We stratified COVID-19 cases by disease severity, defining severe COVID-19 based on hospitalization criteria consistent with international guidelines and Estonian protocols:

(i) *non-severe disease* – SARS-CoV-2 positive individuals with no history of hospitalization due to COVID-19;
(ii) *severe disease* – SARS-CoV-2 positive patients requiring hospitalization but no intensive care during the first 30 days post-infection);
(iii) *critical disease* – SARS-CoV-2 positive patients receiving intensive care during the first 30 days post-infection;
(iv) *lethal disease* – SARS-CoV-2 positive individuals who died during the first 30 days post-infection.

Charlson Comorbidity Index (CCI) quantifies the burden of life-threatening comorbidities by assigning disease-specific weights based on their association with 1-year mortality risk. The cumulative CCI score reflects an individual's overall mortality-predicting disease burden (Charlson Me et al., 1987). Comorbidities for CCI score, its separate components, and particular comorbidities most common in the general population, such as obesity, sleep apnea, hypertension, and hyperlipidemia, were identified and defined by the ICD-10 code occurring at least once on inpatient health care claims or twice occurring over more than 30 days on outpatient health care claims during the year preceding the index date.

Definitions used in Study II

Vaccinated individuals in this study were defined as those who completed a primary SARS-CoV-2 vaccination series with at least two doses of BNT162b2

(Pfizer/BioNTech), mRNA-1273 (Moderna), AZD1222 (Oxford/AstraZeneca), or a single dose of Ad26.COV2.S (Janssen/Johnson & Johnson).

Breakthrough infection was defined as a SARS-CoV-2-positive laboratory test (PCR or antigen test) occurring at least 14 days after the last vaccination.

*Severe breakthrough infectio*n was defined as hospitalization occurring 3 days before to 30 days after a laboratory-confirmed SARS-CoV-2 infection with the presence of at least one specific diagnosis in healthcare claims in relation to hospitalization (U07.1, U07.2, J06, J12, J15-J18, J20-J22, J46, J80–84, J85-J86).

Education level was assessed based on the International Standard Classification of Education, subsequently divided into three levels: basic education or below, general secondary education or vocational education based on secondary education, and higher or tertiary education (Eurostat, n.d.).

Data on *selected chronic comorbid conditions* recorded on healthcare claims during the year before vaccination were included (defined based on ICD-10 diagnosis codes), considering the potential of these diseases to serve as risk factors for severe COVID-19 (see Study II, Appendix A).

Data on hospital stay duration (in weeks) during the year preceding vaccination were included to account for the study participants' frailty (Lingsma et al., 2018).

Definition used in Study III

Vaccination status

Vaccination against COVID-19 was considered as an *exposure* in the analytical framework of the study. Study participants were considered vaccinated if they completed the primary vaccine series: two doses of BNT162b2 (Pfizer/Pfizer/BioNTech), mRNA-1273 (Moderna), AZD1222 (Oxford/AstraZeneca), or one dose of Ad26.COV2.S (Janssen/Johnson & Johnson) 14-180 days before primary SARS-CoV-2 infection. Supplementary doses were not considered.

Outcomes

MACE is a composite of clinical events previously described in various clinical trials aimed at evaluating the effectiveness and safety of cardiovascular interventions (Bosco et al., 2021; Kip et al., 2008; Marsal et al., 2022). We used a *two-point MACE* outcome, defined as a composite of acute myocardial infarction and stroke (including fatal events) occurring 0-365 days after the 1st positive SARS-CoV-2 test. Our focus on two-point MACE in COVID-19 sequelae research is driven by its significant impact on individual and public health levels as a leading cause of mortality and a potential source of long-term disability, reduced quality of life, and premature death. MACE components were defined based on the ICD-10 codes in EHIF data (see Study III, Appendix).

All-cause mortality was defined as death on all causes occurring 0–365 days after the 1st positive SARS-CoV-2 test.

4.4 Statistical analysis

Study I. The statistical analysis involved reporting demographic and health status data as frequencies and proportions for categorical variables, and as means and standard deviations for continuous variables. To identify COVID-19 risk factors, conditional logistic regression was employed, and adjusted (age, gender, comorbidity) OR and 95% confidence intervals (CI) were presented. COVID-19 disease severity groups were compared using chi-squared or Kruskal-Wallis tests. A multinomial logistic regression model, adjusted for age, gender, and Charlson Comorbidity Index (CCI) score, was then computed to derive adjusted relative risk ratios (aRRR) with 95% CIs. The SARS-CoV-2 incidence rate was calculated by dividing the number of SARS-CoV-2 infections by the total person-time at risk. The incidence rate was presented per 10,000 person-months, along with 95% confidence intervals. All analyses were performed in Stata 14.2.

Study II. The statistical analysis involved calculating incidence rates (IRs) of breakthrough infections per 10,000 person-days with 95% Poisson confidence intervals. The distribution of sociodemographic and pre-vaccination health status was assessed, with continuous variables presented as means and standard deviations (SDs) and categorical variables as frequencies and proportions. Missing education level data were imputed using K-nearest neighbour imputation, with age and sex as predictors. To account for the potential effect of SARS-CoV-2 testing frequency, testing propensity was estimated using a negative binomial regression model, with sex, education level, and age as covariates. Factors associated with primary outcomes (age, gender, CCI, and specific comorbidities) were explored using time-dependent Cox regression, with time from the last vaccination as a time-varying covariate. Adjusted models included boosting status and time since the last vaccination as time-varying covariates and all other covariates as non-time-dependent. The results are presented as hazard ratios (HRs) and adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs). All analyses were performed in R version 4.0.3.

Study III. The statistical analysis was based on the TTE framework to approximate causal inference. Descriptive analysis was used to present participant characteristics as means (with standard deviation) for continuous variables and frequencies and percentages for categorical variables. Crude cumulative incidence rates (cIR) were also estimated to assess the influence of age and sex on outcomes. Inverse probability of treatment weighting (IPTW), guided by a directed acyclic graph (DAG), was employed to adjust for confounding variables (age, sex, and comorbidities). To assess the balance of covariates between groups, standardized mean differences (SMD) were calculated. A marginal structural Poisson survival model with penalized splines was then employed to assess the time-varying effects of vaccination on MACE and all-cause mortality. The treatment effects were evaluated using weighted incidence rate ratios (wIRR) averaged over the one-year follow-up period. This approach avoids the proportional hazards assumption and accounts for non-linear, time-dependent relationships. All analyses were conducted in R.

4.5 Ethical considerations

All studies included in this dissertation received ethical approval from the Research Ethics Committee of the University of Tartu, which waived the need for informed consent due to the retrospective nature of the studies and the exclusive use of de-identified, registry-based data, which ensured anonymity. We received approval from the Estonian Committee on Bioethics and Human Research for data collection from the Health and Welfare Information Systems Centre (TEHIK).

5. MAIN RESULTS

5.1 Individual-level risk factors for primary SARS-CoV-2 infection in vaccinated and unvaccinated populations

5.1.1 Description of the study sample: unvaccinated cohort (Study I)

The average age of SARS-CoV-2 infected individuals (n=66,295) was 44.1 years (SD 20.6), compared to 42.3 years (SD 22.9) in the control group (n=254,958) ($p<0.001$). Most individuals infected with SARS-CoV-2 were under 60 years old (76.5%), with a similar distribution of SARS-CoV-2 positivity across 10-year age groups (16-23%), and a slightly lower prevalence of infection among those under 9 years old (8,5%).

The proportion of females was higher among individuals with SARS-CoV-2 infection (54%) compared to the control group (51.2%, $p < 0.001$).

Both SARS-CoV-2-infected and uninfected individuals were relatively healthy, with no significant comorbidities (CCI = 0) in 89.8% of COVID-19 cases and 92.7% of individuals in the reference cohort. The CCI mean score was slightly higher among individuals with SARS-CoV-2 infection (0.15 [SD 0.52] vs 0.11 [SD 0.43], $p<0.001$). Hypertension and hyperlipidaemia were the most prevalent comorbidities among the studied individuals, with a greater prevalence among SARS-CoV-2-infected individuals (18.4% vs. 14.6%, $p < 0.001$, and 3.5% vs. 2.8%, $p < 0.001$, respectively). Congestive heart failure (2.3% vs 1.7%, $p<0.001$), cerebrovascular disease (0.9% vs 0.5%, $p<0.001$), dementia (0.7% vs 0.2%, $p<0.001$), chronic pulmonary disease (1.6% vs 1.3%, $p<0.001$), chronic kidney disease (0,3% vs 0,1%, $p<0.001$), cancer (2% vs 1.5%, $p<0.001$), liver disease (0.3 % vs 0.2%, $p<0.001$), obesity (1.8 % vs 1%, $p<0.001$), and diabetes (2.2% vs 1.6%, $p<0.001$) were also more prevalent among SARS-CoV-2 infected individuals than among control group (see Tabel 1 in Study I).

During the study period, 6032 individuals from the control group tested positive for SARS-CoV-2, resulting in IR of 116.99 (95% CI 114.08–119.98) per 10,000 person-months. This means that, on average, Estonia recorded approximately 117 new SARS-CoV-2 cases per 10,000 people each month, totaling over 15,000 cases per month during the observed period.

5.1.2 Description of the study sample: vaccinated cohort (Study II)

Data on a cohort of 184,132 individuals with no documented history of SARS-CoV-2 infection who had completed a primary COVID-19 vaccination series were analysed to explore the incidence and risk factors for breakthrough SARS-CoV-2 infection and breakthrough COVID-19 severity over an 11-month follow-up period.

The mean age of the individuals included in the cohort was 48.9 years (SD 19.9), with 54% being female. Most participants (80.8%) had either medium or high levels of education. Regarding health status, 84.7% of individuals had no significant comorbidities, as indicated by a CCI score of 0. Only 12.4% had a CCI of 1–2, and 2.9% had a CCI of 3 or higher. The most frequent comorbid chronic conditions were hypertension (27.8%), mood disorders (7.9%), diabetes (6.6%), chronic heart diseases (6.2%), and chronic lung diseases (4.5%).

During the 11-month follow-up, 29,688 individuals (16% of vaccinated cohort) experienced BTI, with an IR of 8.03 (95% CI 7.95–8.13) per 10,000 person-days and a median follow-up time to first BTI of 7 months (range 0–386 days).

5.1.3 Individual-level risk factors for SARS-CoV-2 infection in the unvaccinated population (Study I)

Multivariable logistic regression analysis revealed that women had slightly higher odds of testing positive for SARS-CoV-2 compared to men (aOR 1.1, 95% CI 1.08 – 1.12).

Age had only a modest impact on the likelihood of acquiring SARS-CoV-2 infection, with an aOR of 1.02 (95% CI 1.02 – 1.03) for every ten-year increase in age. Compared to adults aged 30–39 years, both young children and older individuals were significantly less likely to be infected. Children under 9 years had the lowest risk (aOR 0.34, 95% CI 0.32 – 0.35). Among adults, those aged 70 – 79 had an aOR of 0.61 (95% CI 0.59 – 0.64), and those aged 80–89 had an aOR of 0.78 (95% CI 0.74 – 0.81), indicating a lower infection risk in these age groups as well (see Fig. 4).

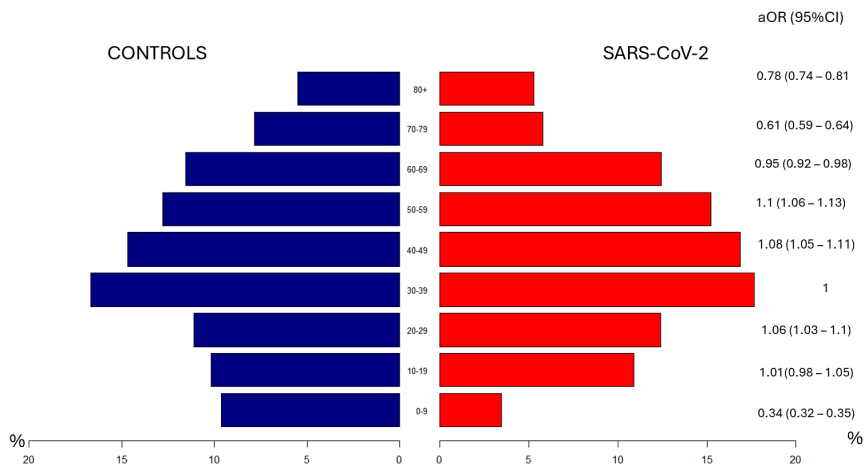

Figure 4. Age-specific SARS-CoV-2 infection: proportions and adjusted odds ratios with 95% confidence intervals in Estonia, Feb 2020 – Feb 2021

A higher comorbidity burden, as indicated by the CCI score, was linked to an increased risk of SARS-CoV-2 infection. Compared to individuals with a CCI score of 0, those with a score of 1-2 had an adjusted odds ratio (aOR) of 1.31 (95% CI 1.26–1.36) for infection. The risk rose further for individuals with a CCI score of 3 or higher, with an aOR of 1.47 (95% CI 1.4–1.54).

Risk of SARS-CoV-2 infection was significantly higher in case of various comorbid conditions, with the strongest association with dementia (OR 3.77, 95% CI 3.3-4.31), kidney disease (OR 1.88, 95% CI 1.56-2.26), and cerebrovascular disease (OR 1.81, 95% CI 1.64-2), followed by obesity (OR 1.61, 95% CI 1.5-1.73), liver disease (OR 1.58, 95% CI 1.33-1.87), diabetes (OR 1.33, 95% CI 1.25-1.41), cancer (OR 1.27, 95% CI 1.19-1.35), peptic ulcer disease (OR 1.27, 95%CI 1.05-1.54), chronic pulmonary disease (OR 1.24, 95% CI 1.16-1.33), and congestive heart failure (OR 1.22, 95% CI 1.15-1.29), hypertension (OR 1.19, 95% CI 1.16-1.23), and lipid disorder (OR 1.11, 95% CI 1.05-1.16). We didn't find an association between AIDS or rheumatologic diseases and the risk of SARS-CoV-2 infection ($p > 0.05$).

5.1.4 Individual-level risk factors for SARS-CoV-2 infection in the vaccinated population (Study II)

Females had a slightly higher risk for BTI than males (aHR 1.12, 95% CI 1.09–1.15). Compared to those under 40 years of age, individuals aged 50–59 had a lower risk (aHR 0.75, 95% CI 0.69–0.82) of BTI, with the risk decreasing further in older age groups (aHR 0.34 for ages 70–79 and aHR 0.31 for ≥80).

Medium (aHR 0.89, 95% CI 0.86–0.92) and high educational level (aHR 0.90, 95% CI 0.85–0.95) were associated with a modestly reduced risk of BTI.

A slightly increased risk of breakthrough infection (BTI) was observed only among individuals with a high comorbidity burden, as indicated by CCI score of ≥3 (aHR 1.18, 95% CI 1.05–1.33). Among specific conditions, dementia was associated with the highest risk (aHR 1.69, 95% CI 1.40–2.04), followed by chronic kidney disease (aHR 1.16, 95% CI 1.01–1.34), chronic lung disease (aHR 1.14, 95% CI 1.07–1.22), and heart disease (aHR 1.10, 95% CI 1.02–1.18).

No statistically significant association with BTI was observed for hypertension, diabetes, obesity, cerebrovascular disease, mood disorders, malignancies, chronic liver disease, or rheumatologic conditions.

5.2 Individual-level risk factors for severe COVID-19 among unvaccinated and vaccinated individuals

5.2.1 Distribution of COVID-19 severity in unvaccinated SARS-CoV-2 infected individuals

Most SARS-CoV-2-infected individuals (92%, n=60,845) experienced a non-severe course of the disease (they did not need hospitalization due to SARS-CoV-

2 infection). Demographic analysis revealed that approximately half of the individuals with non-severe disease were females (54%), with a mean age of 42.0 years. Most of this cohort (65.2%) consisted of individuals younger than 50 years with no history of significant comorbidities (CCI = 0 in 92%), and only 7.5% had one or more comorbid conditions.

About 4.8% (n=3,198) of the study population experienced severe illness that required hospitalization but not intensive care. Among these patients, 57.4% were females, with a mean age of 62.9 years. Nearly a quarter (23.7%) were under 50 years of age, and one-third had significant co-morbid conditions (CCI ≥1).

A total of 1,7% (n=1,129) of patients progressed to critical illness requiring intensive care. These patients had a mean age of 67.3 years, with males making up slightly more than half of the group (55.8%). The majority of those critically ill with COVID-19 were people aged 60 years and older (73,5%). Notably, 12.7% of critically ill patients were under the age of 50 years. Fewer than half of critically ill individuals (41%) had significant pre-existing comorbidities (CCI≥1). The median length of stay in intensive care was 17 days, significantly longer than the 8-day median for patients hospitalized without requiring intensive care ($p < 0.001$).

There were 970 (1,5%) individuals who died within the first 30 days after testing positive for SARS-CoV-2 infection. They had an average age of 80.9 years, with two-thirds of the deaths occurring in those aged 80 years or older. Deaths among individuals younger than 50 years were infrequent, accounting for 1.4% of all deaths. More than half (58.3%) of those who died with COVID-19 had at least one or more co-morbid conditions (CCI≥1). These individuals had the shortest hospital stays, with a median of 6 days, indicating that the most severe and intense COVID-19 cases progressed the fastest.

The overall IR of severe COVID-19 cases in the unvaccinated cohort was 15.9 (95%CI 5,5 – 16,4) per 10,000 person-days. On average, about 16 individuals out of every 10,000 infected individuals necessitated hospitalization each day.

5.2.2 Individual-level risk factors for severe COVID-19 in unvaccinated individuals

A definitive dose-response relationship exists between age and the severity of COVID-19. As age progresses, the likelihood of experiencing severe clinical outcomes correspondingly increases, with the escalation in risk being particularly pronounced for lethal outcome among older populations (See Fig.3, panel A).

In multinomial logistic regression analysis, age exhibited the strongest correlation with COVID-19 severity, with RRR (relative risk ratio) of 1.68 (95% CI 1.65–1.72) for hospitalization, RRR 1.97 (95%CI 1.90–2.05), for intensive care, and RRR 3.91 (95%CI 3.70–4.19) lethal outcome, all compared to individuals with non-severe COVID-19, for every 10-year increase in age.

Individuals aged 50–59 years were twice as likely to develop severe disease (RRR 2.43, 95% CI 2.16–2.73), four times more likely to require intensive care (RRR 4.46, 95% CI 3.55–5.6), and almost nine times more likely to die (RRR

8.61, 95% CI 4.56–16.25) compared to those under 50 years old. The risk of severe disease was exponentially increasing with every decade of life, achieving RRR 4.43 (95%CI 3.97–4.94) in those 60–69 y.o 0, RRR 9.51 (95%CI 8.44–10.71) in those 70–70 y.o., and RRR 16.55 (95%CI 14.69–18.65) in those 80 y. and above.

Compared to those under 50 years old, the risk of death was significantly higher among individuals aged 70-79 years (RRR 172.98, 95% CI 100.26–298.46) and 80-89 years (RRR 784.11, 95% CI 485.38-1341.3).

The protective effect of female sex was substantial, with the strength of association increasing with disease severity. Thus, being female lowered the risk of hospitalization to 0.84 (95% CI 0.78-0.91), the risk of requiring intensive care to 0.44 (95% CI 0.39–0.50), and the risk of a lethal outcome to 0.41 (95% CI 0.35–0.47).

A higher CCI score was associated with an increased risk of severe COVID-19 outcomes. Compared to a CCI score of 0, a score of 1-2 was associated with a 63% higher risk of hospitalization (RRR 1.63, 95% CI 1.46–1.83) A score of 3 or higher was associated with more than twice the risk of hospitalization (RRR 2.65, 95% CI 2.34-2.99), more than three times the risk of requiring intensive care (RRR 3.87, 95% CI 3.27–4.58), and more than four times the risk of a lethal outcome (RRR 4.59, 95% CI 3.84–5.48) (See Fig. 5, panel B).

Almost all assessed comorbid conditions exhibited a strong association with severe COVID-19 outcomes. Kidney disease emerged as the strongest predictor, with aRRR of 5.41 (95% CI, 3.59–8.13) for hospitalization and 7.71 (95% CI, 4.71–12.62) for critical care necessity. Similarly, AIDS was associated with a RRR of 5.01 (95% CI, 1.08–23.12) for hospitalization and 16.77 (95% CI, 3.53–79.79) for critical illness. Other conditions associated with at least a twofold increase in the risk of hospitalization – and up to a threefold increase in the risk of critical illness – included cancer, peripheral vascular disease, chronic pulmonary disease, peptic ulcer disease, liver disease, and cerebrovascular disease. Additionally, obesity, sleep apnea, diabetes, myocardial infarction, and congestive heart failure were linked to up to a twofold increase in hospitalization risk (see Table 3, Study I)

Kidney disease, cerebrovascular disease, chronic pulmonary disease, peptic ulcer disease, cancer, and liver disease were each associated with more than a twofold increase in the risk of death within one month of SARS-CoV-2 infection. Among these, kidney disease conferred the highest mortality risk, with an adjusted relative risk ratio (aRRR) of 6.48 (95% CI, 3.74–11.23). Notably, dementia was associated with a reduced likelihood of receiving treatment in the intensive care unit (RRR 0.38, 95% CI 0.21–0.69), but a significantly higher risk of death (RRR 1.85, 95% CI 1.43–2.45) (see Figure 3, panel C). A history of influenza infection within the two years preceding SARS-CoV-2 infection was linked to a modestly increased risk of severe COVID-19 (RRR 1.22, 95% CI 1.13–1.33).

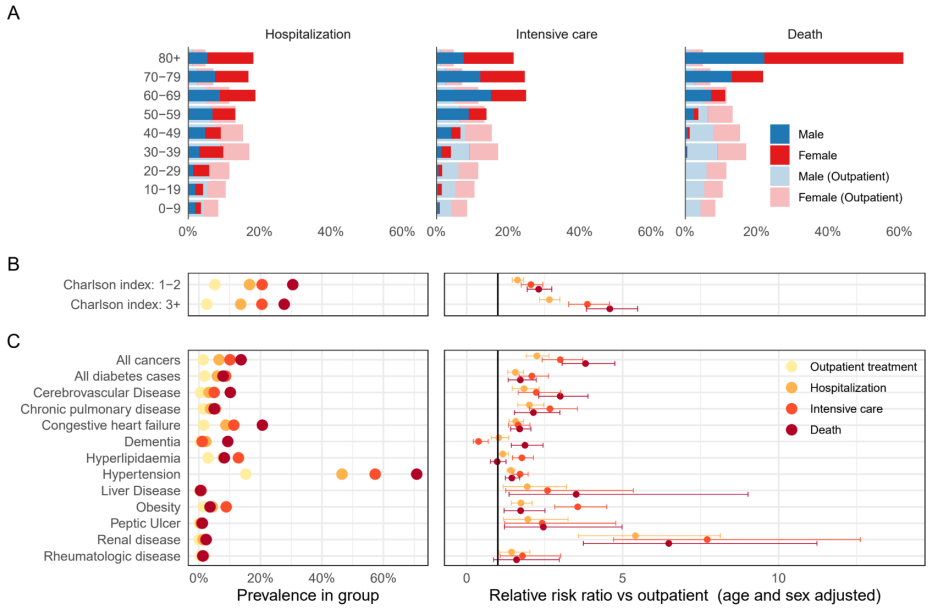

Figure 5. Distribution of COVID-19 outcomes, along with relative risk estimates for severe disease progression, Estonia, February 2020 – February 2021
A. Distribution of COVID-19 outcomes (outpatient, hospitalization, intensive care, and death) across sexes and ages. The proportion of outpatient individuals is duplicated across the three separate diagrams (hospitalization, intensive care, and death), resulting in overlapping representations intended to facilitate comparison within each age group.
B. Prevalence of individuals with different comorbidity burden according to CCI score across groups with different COVID-19 severity (left-sided picture) and relative risk ratio (RRR) of severe COVID-19 outcomes in these subgroups adjusted for age and sex.
C. Prevalence of individuals with specific comorbidities across groups with different COVID-19 severity (left-sided picture) and relative risk ratio (RRRs) for severe outcomes (hospitalization, intensive care, and death) in these subgroups adjusted for age and sex.

5.2.3 Incidence and individual-level risk factors for severe COVID-19 in vaccinated individuals

Severe COVID-19 requiring hospitalization occurred in 355 (1,2 %) of vaccinated individuals with BTI, corresponding to IR of 4.03 (95% CI 3.63 - 4.48 per 10,000 person-days). In the entire vaccinated cohort IR of severe COVID-19 was 0.093 (95% CI 0.084–0.104 per 10,000 person-days).

The crude mortality rate among severely ill vaccinated individuals with COVID-19 was 15.2%. Female sex had a protective role against severe BTI (aHR 0.68, 95% CI 0.55–0.84).

Age emerged as a significant determinant of severe outcomes, with the risk of hospitalization increasing progressively from the age of 50 years. Compared to younger individuals, those aged 60–69 had a nearly threefold increased risk (aHR

2.85, 95% CI 1.76–4.61), which rose to almost fourfold among those aged 70–79 (aHR 3.87, 95% CI 2.37–6.32), and exceeded sevenfold in individuals aged 80 years and older (aHR 7.23, 95% CI 4.36–12.02). (See Fig. 6)

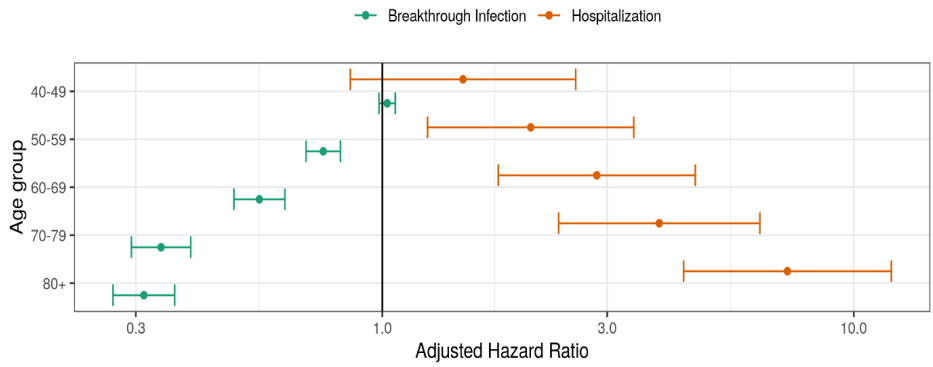

Figure 6. Adjusted hazard ratios (aHR) for SARS-CoV-2 breakthrough infection and COVID-19 hospitalization by age group in Estonia, January 2021 – February 2022

There was no association between level of education and the risk of COVID-19 severity in vaccinated individuals.

Comorbidity burden emerged as a significant predictor of hospitalization risk among vaccinated individuals with BTI. Specifically, individuals with a CCI score of 1–2 demonstrated an approximately twofold increase in the risk of hospitalization (aHR 2.09, 95% CI 1.54–2.83), and this risk was slightly higher for those with a CCI score of ≥3 (aHR 2.23, 95% CI 1.43–3.50).

Among specific conditions, chronic liver disease (aHR 2.0, 95%CI 1.11–3.61), chronic kidney disease (aHR 1.92, 95%CI, 1.32–2.8), cerebrovascular diseases (aHR 1.72, 95%CI 1.11–2.67), chronic lung diseases (aHR 1.72, 95%CI, 1.28–2.31), diabetes (aHR 1.71, 95%CI 1.29–2.27) heart diseases (aHR 1.34, 95%CI 1.02–1.76), and cancers (aHR 1.42, 95%CI, 1.04–1.94) were all significantly associated with increased risk of severe infection and hospitalization in vaccinated individuals. Dementia was not related to the risk of hospitalization among patients with breakthrough infection (aHR 1.52, 95% CI 0.88–2.61).

5.2.4 Impact of booster vaccine dose on breakthrough infection and COVID-19 severity

Nearly half of the cohort (46.7%) received a booster COVID-19 vaccine dose, administered on average 6 months (median, 199 days) after completing the primary vaccination series.

Compared to individuals who received only the primary COVID-19 vaccination series, those who received a booster dose had markedly lower rates of breakthrough infection (6% vs. 25%) and hospitalization due to severe BTI

(0.03% vs. 0.33%). Although the booster dose offered only modest additional protection against breakthrough infection (aHR 0.95, 95% CI 0.90–0.99), it was strongly protective against severe disease, reducing the risk of severe COVID-19 in vaccinated individuals with breakthrough infection by 68% (aHR 0.32, 95%CI 0.19–0.54).

5.2.5 Duration of vaccine-induced immunity against SARS-CoV-2 infection and severe COVID-19

The risk of BTI increased with time since vaccination (See Fix 3). It began to rise two months after the last dose (aHR 1.21, 95% CI 1.16–1.27) and peaked at four months (aHR 1.75, 95% CI 1.66–1.83). The risk of severe BTI remained low for up to six months after vaccination with aHR 1.74 (95% CI 1.05–2.90) for hospitalization starting from six months post-vaccination (See Fig. 7)

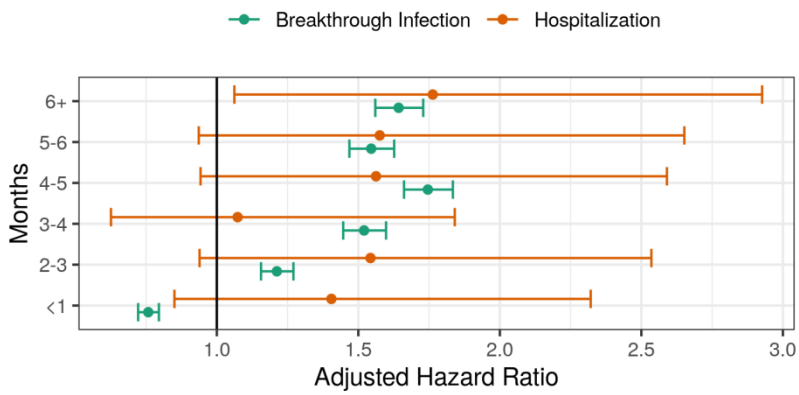

Figure 7. Adjusted hazard ratios (aHR) for breakthrough SARS-CoV-2 infection and progression to severe COVID-19 over time, measured in months since the last vaccine dose; Estonia, January 2021 – February 2022

5.3 Effect of COVID-19 vaccination on post-COVID-19 MACE and mortality

5.3.1 Description of study population

In total, 33,554 individuals aged 40–85 years who were infected with SARS-CoV-2 between April 2021 and May 2022 were eligible for the target trial analysis. Of them, 18,223 were vaccinated with a complete COVID-19 vaccine series, and 15,331 were unvaccinated prior to their first positive SARS-CoV-2 test.

The vaccinated and unvaccinated groups were comparable in terms of sex distribution, with 42.2% male and 57.8% female participants in each group. The vaccinated group had a slightly higher mean age (55.0 years) compared to the

unvaccinated group (54.0 years). A difference in COVID-19 severity was observed, with 2.8% of unvaccinated individuals developing severe disease compared to 0.5% of vaccinated individuals ($p < 0.001$). This corresponds to a moderate effect size, with SMD for both severe and non-severe COVID-19 outcomes being approximately 0.20.

Additionally, a greater proportion of individuals in the vaccinated group were over 70 years old (11.4% vs. 9.2%). However, the difference in age distribution was of small magnitude (SMD < 0.1) and is unlikely to have introduced substantial bias in subsequent analyses.

A notable imbalance was observed between the vaccinated and unvaccinated cohorts in terms of mother tongue, educational level, and county of residence. For instance, 39.3% of vaccinated individuals had higher education, compared to only 22.7% among the unvaccinated. Additionally, 68.4% of vaccinated individuals reported Estonian as their mother tongue, whereas 50.7% of unvaccinated individuals reported a non-Estonian mother tongue. These differences were substantial (SMD = 0.4), indicating a meaningful imbalance across these sociodemographic variables.

In contrast, comorbidity profiles were generally similar between the groups. Heart disease was slightly more prevalent among vaccinated individuals (39.5% vs. 35.9%), as was diabetes (8.0% vs. 7.0%), though these differences were minor (SMD < 0.1). The prevalence of chronic lung disease was identical in both groups (10.0%), also reflecting negligible imbalance (SMD < 0.1).

After applying IPTW, all covariates achieved good balance (SMD < 0.1), thereby enhancing the validity of the subsequent causal analysis.

5.3.2 Incidence of MACE and mortality

During the follow-up period, 321 new cases of major adverse cardiovascular events (MACE) were recorded: 170 cases (0.9%) occurred among vaccinated individuals and 151 cases (1.0%) among the unvaccinated. A total of 1,494 individuals (4.5%) had a follow-up period shorter than 365 days. Among them, 19 (1,9%) vaccinated individuals and 7 (1,4%) unvaccinated individuals developed MACE.

The cIR for MACE was slightly lower in the vaccinated group at 0.95 per 100 person-years (95% CI 0.82–1.10), compared to 1.01 (95% CI 0.86–1.19) in the unvaccinated. A clear sex-related difference regarding MACE incidence was observed. Males consistently exhibited higher cIRs than females in both cohorts: cIR 1.37 (95% CI 1.13–1.66) vs 0.64 (95% CI 0.51–0.82) in vaccinated and cIR of 1.21 (95% CI 0.97–1.52) vs cIR 0.87 (95% CI 0.69–1.09) in the unvaccinated cohort.

MACE events were temporally dispersed, with only 41% occurring within the first 90 days post-infection and a median time to event of 123 days, indicating a delayed onset rather than an acute response.

A total of 640 all-cause deaths were recorded during the follow-up, with nearly twice as many occurring among unvaccinated individuals: 253 deaths (1.4%) in the vaccinated group and 387 deaths (2.5%) in the unvaccinated group.

The overall cIR for all-cause death was 1.41 (95% CI 1.25–1.59) per 100 person-years in the vaccinated group, compared to 2.59 (95% CI 2.34–2.85) in the unvaccinated. This pattern was consistent across both sexes, though the difference between vaccinated and unvaccinated individuals was more pronounced in women. Among men, cIR was 2.16 (95% CI: 1.85–2.51) in the vaccinated group, compared to 3.13 (95% CI: 2.72–3.58) in the unvaccinated group. In women, the cIR was substantially lower in the vaccinated group at 0.87 (95% CI: 0.71–1.07), versus 2.29 (95% CI: 1.91–2.53) in the unvaccinated.

Most deaths occurred shortly after being infected with SARS-CoV-2, with 60% taking place within the first 90 days and a median time to death of 53 days, indicating a sharp early peak in mortality after infection.

5.3.3 Causal inference of vaccination on post-COVID-19 MACE

The overall effect

The overall wIRR for MACE was 0.71 (95% CI 0.58–0.84), indicating a 29% reduction in the risk of MACE among vaccinated individuals.

Time-varying sex and age-dependent effects of vaccination on MACE incidence

The protective effect of vaccination was most evident during the first three months following the primary vaccination series, eventually converging after that (Fig. 8, panel A). Temporal trends showed that unvaccinated females (Fig. 8, panels C–E.) and younger unvaccinated males (Fig. 8, panel B) experienced a sharp spike in MACE incidence immediately after SARS-CoV-2 infection, with rates approximately three times higher than their vaccinated counterparts. These rates declined over the first three months, replicating the impact of vaccination in the whole cohort.

Among older males, the initial incidence of MACE following SARS-CoV-2 infection was similar between vaccinated and unvaccinated individuals, and also consistent with rates observed in vaccinated females of the same age group (Fig.8, panels D–E). However, a delayed increase in MACE incidence was noted among vaccinated older males, peaking approximately two months post-infection. This elevated risk subsequently declined, aligning with the incidence observed in the unvaccinated cohort by the fourth month post-infection.

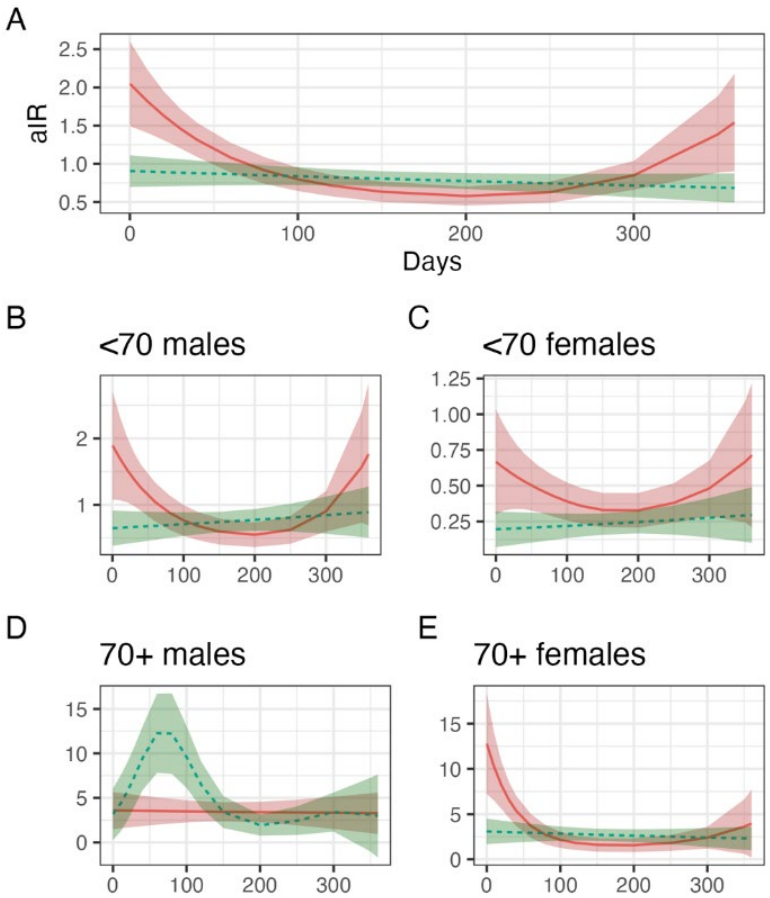

Figure 8. MACE rates for the vaccinated and the unvaccinated over the study follow-up period.

The vaccinated rates are denoted with green dotted lines, and the unvaccinated rates are in continuous red lines. Shaded areas represent 95% confidence intervals. A. MACE rates for the full study population. B.-E. MACE rates for populations stratified by sex and age. B. < 70-year-old males; C. < 70-year-old females; D.> 70males; E. > 70 females. The X-axis shows time from baseline (T0) in days, and the Y-axis plots the incidence rate per 100 person-years.

Sex and age-dependent causal inference of vaccination on MACE risk

Sex- and age-stratified analyses revealed distinct patterns in the protective effect of vaccination against MACE. Among females aged ≤70 years, vaccination was associated with a substantial 54% reduction in MACE risk (wIRR 0.46, 95% CI: 0.27–0.64). A similar, though more modest, 30% reduction was observed in younger males (wIRR 0.70, 95% CI: 0.50–0.91). Older females (>70 years) also

experienced a significant benefit, with a 40% lower risk of MACE (wIRR 0.60, 95% CI: 0.39–0.82). In contrast, no protective effect was observed in males over 70 years; instead, this group showed a non-significant trend toward increased MACE incidence (wIRR 1.66, 95% CI: 0.95–2.37).

Subgroup analysis among people with non-severe COVID-19

Among individuals who experienced non-severe COVID-19, the vaccination effect was comparable to that of the whole cohort and revealed a reduced risk of MACE in this subgroup (wIRR 0.73, 95% CI 0.59–0.87). When stratified by sex, this protective association was particularly evident among females, with a wIRR of 0.55 (95% CI 0.40–0.70). In contrast, no significant reduction in MACE risk was observed among males (wIRR 1.09, 95% CI 0.84–1.35), suggesting a potential sex-specific difference in vaccine-associated cardiovascular protection in the subgroup of people with non-severe COVID-19.

Given the limited number of MACE cases (n = 8) observed in the severe COVID-19 subgroup, the statistical power was insufficient to support robust analysis. Thus, no definitive conclusions could be drawn for this population.

5.3.4 Causal inference of vaccination on post-COVID-19 all-cause mortality

Overall effect

Our analysis revealed that COVID-19 vaccination was associated with a substantial reduction in all-cause mortality. The overall wIRR was 0.32 (95% CI: 0.28–0.36), indicating a 68% lower risk of death among vaccinated individuals compared to their unvaccinated counterparts (Figure 9, panel A)

Time-varying sex and age-dependent effects of vaccination on post-COVID-19 mortality

Temporal trends demonstrated that unvaccinated individuals experienced markedly elevated mortality rates shortly after SARS-CoV-2 infection (Fig. 9, panel A). These rates declined exponentially over time, reaching levels comparable to those observed in vaccinated individuals approximately 90 to 100 days post-infection, in both females and males (Fig. 9, panels B–E). Notably, among unvaccinated males over 70 years of age, mortality rates were more than twice as high as those observed in unvaccinated females of the same age group. This pattern was not seen among vaccinated individuals. Vaccination conferred a 5- to 10-fold reduction in the initial mortality rate in this high-risk subgroup.

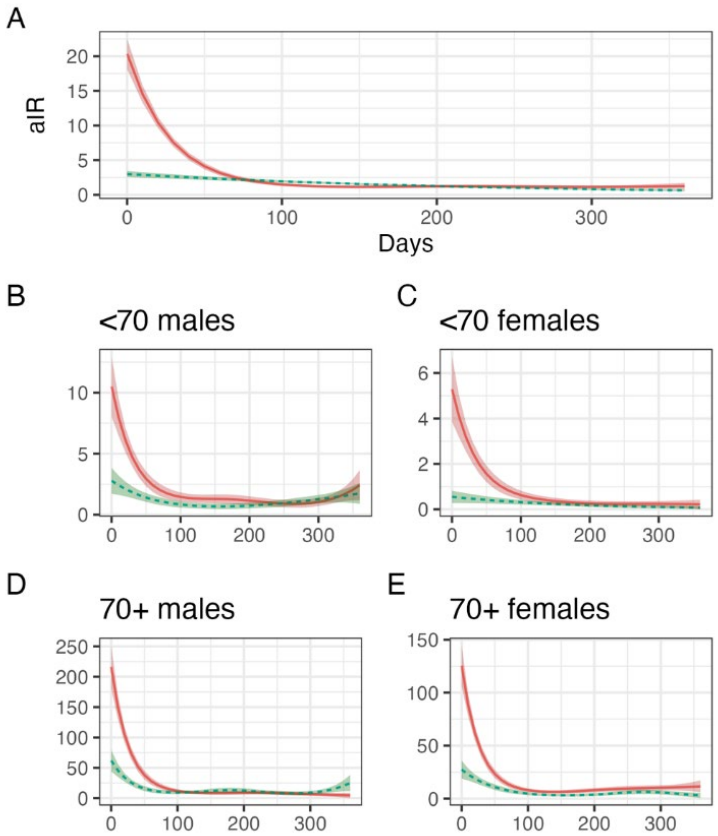

Figure 9. All-cause death rates for the vaccinated and the unvaccinated over the study follow-up period. The vaccinated rates are denoted with green dotted lines, and the unvaccinated are in continuous red lines. Shaded areas represent 95% confidence intervals. A. *All-cause death* rate for the full study population. B.-E. *All-cause death* rates for populations stratified by sex and age. B. < 70-year-old males; C. < 70-year-old females; D. >70 males; E. 70+ females. The X-axis shows time from baseline (T0) in days, and the Y-axis plots the incidence rate per 100 person-years.

Sex- and Age-Stratified Causal Inference of Vaccination on Mortality Risk

The protective effect of vaccination against all-cause mortality was consistent across sex and age groups. Among females, the overall wIRR was 0.36 (95% CI: 0.30–0.43), with a more pronounced effect observed in those aged ≤70 years (wIRR 0.18, 95% CI 0.09–0.27) compared to those over 70 years (wIRR 0.33, 95% CI 0.25–0.42). Similarly, males exhibited a significant reduction in mortality risk (wIRR 0.44, 95% CI 0.38–0.50), with a slightly stronger effect in those over 70 years (wIRR: 0.31, 95% CI 0.24–0.39) than in younger males (wIRR 0.48, 95% CI: 0.36–0.60).

Subgroup analysis among individuals with non-severe COVID-19

Among individuals with non-severe COVID-19, the protective effect of vaccination on all-cause mortality mirrored that observed in the overall cohort. In this subgroup, the wIRR was 0.35 (95% CI 0.27–0.43) for females and 0.45 (95% CI 0.37–0.53) for males, reinforcing the consistent benefit of vaccination for those with milder disease course.

Due to the limited number of deaths among vaccinated individuals with severe COVID-19 (n = 86), the statistical power was insufficient to conduct a robust analysis. However, no definitive conclusions could be drawn for this subgroup.

6. DISCUSSION

This doctoral thesis presents a comprehensive, population-based analysis of the clinical and epidemiological aspects of COVID-19 in Estonia, with a particular emphasis on the role of vaccination. The research demonstrates that while advanced age, male sex, and comorbidities were primary risk factors for severe outcomes in both unvaccinated and vaccinated individuals, vaccination significantly attenuated their impact. Crucially, the protective effect of vaccination against major post-COVID-19 sequelae was time-limited and varied by age and sex, revealing a dynamic interplay between vaccine-induced immunity and individual vulnerability. These findings highlight both the multifaceted impact and the temporal limitations of COVID-19 vaccination, underscoring the need for risk-stratified strategies – before and after infection – to protect vulnerable populations and guide preparedness for future pandemics.

6.1 Individual-level risk factors for SARS-CoV-2 infection among vaccinated and unvaccinated populations.

This analysis reveals that while some risk factors for infection remain consistent, vaccination alters the risk profile for a subsequent SARS-CoV-2 infection.

There was a modest, non-linear association between age and the risk of SARS-CoV-2 infection in the unvaccinated cohort, with both the youngest and oldest groups showing lower odds compared to middle-aged adults. This suggests a possible bias related to the testing strategy and underreporting of milder cases in younger children (Choi et al., 2022). Evidence from other studies suggests that differences in infection rates are likely attributable to behavioral and social factors rather than biological susceptibility alone. Thus, studies in rural populations with lower population density and lower obligatory social contacts have shown a lower incidence of SARS-CoV-2 infections at the beginning of the pandemic (Cuadros et al., 2021). In Estonia, the closure of educational institutions from March 2020 to May 2021 – with intermittent attempts to restore contact learning – significantly limited children's exposure opportunities, particularly for those in primary education (Lutsar & Emor, 2023). In contrast, participating in essential services during the pandemic and assuming caregiving responsibilities for children and elderly family members may increase the frequency of interpersonal contact among working-age individuals, thereby elevating their risk of exposure. In this context, age functions as a proxy for varying levels of social interaction, mobility, and adherence to public health measures, which significantly influence the likelihood of SARS-CoV-2 transmission. The protective effect of advanced age was even more pronounced for breakthrough infections in the vaccinated cohort, as BTIs were predominantly observed in younger adults. This finding is consistent with other studies on risk factors for breakthrough infections (Antonelli, Penfold, et al., 2022). Notably, half of all BTIs occurred in

individuals under 40 years old, and 84.5% of these cases were in those under 60, highlighting higher levels of social interaction in the working-age population and the rapid relaxation of public health restrictions following the rollout of mass vaccination strategies targeting the working population. The inverse relationship between advanced age and the risk of SARS-CoV-2 infection may reflect naturally reduced social activity due to retirement status and the absence of childcare responsibilities among older individuals, as well as greater adherence to protective measures such as physical distancing, mask use, and self-isolation, which were targeted at older and vulnerable populations (Wachira et al., 2023). Notably, it presents an interesting contrast to vaccine effectiveness trials, which demonstrated reduced vaccine effectiveness in older adults compared to younger populations, attributed to immune system senescence and a generally weaker immune response following vaccination in this group (Andrews et al., 2022; Bachmann et al., 2025).

Women were slightly more likely to have SARS-CoV-2 infection, a pattern that remained consistent among vaccinated individuals with breakthrough infection. This finding may reflect differences in health-seeking behavior among genders, including testing frequency, social activity, and occupational exposure (Auderset et al., 2024). Thus, women comprise approximately 70% of the global health workforce and 95% of nurses and care workers in Estonia, illustrating a significant gendered concentration in frontline healthcare positions (Estonian Institute for Health Development, n.d.-b). Women's predominance in high-contact care roles, both within formal healthcare settings and in informal caregiving capacities, places them at elevated risk of exposure to infectious diseases such as COVID-19 (Diktas et al., 2021; Dzinamarira et al., 2022; European Institute for Gender Equality, 2022; WHO, 2019). This pattern of disproportionate exposure among women healthcare workers has also been observed in past outbreaks, including Ebola, H1N1, and the 1918 influenza pandemic (Balkhy et al., 2010; Davies & Bennett, 2016; Morgan et al., 2022).

In the vaccinated cohort, higher levels of education were associated with a lower risk of SARS-CoV-2 infection. This relationship may be partly explained by the increased likelihood of remote work opportunities among individuals with higher education, which were less accessible to those in lower-skilled occupations. On the other hand, studies investigating compliance with COVID-19 containment methods have consistently demonstrated lower engagement in COVID-19 preventive behaviors, lower risk perception, and lower trust in scientists among people with lower education levels. A study on adherence to COVID-19 restriction measures in Estonia confirms that individuals with lower education levels, younger people, those with financial constraints, and individuals at high risk of alcohol consumption were less likely to follow the restrictions implemented to contain the spread of the virus. Ethnicity and language were not significant predictors (Tulviste et al., 2025). Furthermore, residing in regions with higher vaccine hesitancy was linked to increased rates of breakthrough infections in other study (Anzalone, Sun, et al., 2023). Additionally, several psychological factors, such as perceived danger, self-efficacy, trust in others, and sense of

belonging (sense of community), were considered essential modulators of compliance and infection risk (Chong et al., 2023; Sarracino et al., 2024; Tulviste et al., 2025).

These factors may contribute to real-world vaccine effectiveness by modulating the risk of infection while the pandemic evolves. Thus, considering behavioral, occupational, psychological, and sociodemographic patterns is essential when assessing incident infections, as understanding individual-level risk factors for both primary SARS-CoV-2 infection and BTI is key to informing targeted prevention strategies and optimizing vaccine deployment.

The most significant differences between vaccinated and unvaccinated individuals lie in the impact of comorbidities, as vaccination has dramatically changed the role of comorbidities as a risk factor. In the unvaccinated population, numerous chronic conditions like hypertension, diabetes, and cerebrovascular disease were significantly associated with an increased risk of infection. In contrast, among vaccinated individuals, most of these specific comorbidities no longer posed a significant risk for breakthrough infection. Only a high burden of comorbidity and a few particular conditions, like dementia or heart diseases, were found to increase the risk. This suggests that vaccination effectively mitigates the heightened risk of infection previously associated with a wide range of underlying health issues.

Dementia emerged as the most substantial risk factor of SARS-CoV-2 infection, regardless of vaccination status. As we were not able to account for testing frequency in the first study on the unvaccinated cohort, there is a potential for bias due to a high prevalence (up to one-third) of individuals with dementia in nursing homes (National Institute for Health Development, n.d.-b), where mass-testing strategies may have increased the likelihood of detecting infections in this group. However, in the vaccinated cohort, the results were adjusted for testing intensity, thereby reducing potential bias introduced by differential testing practices in residential settings. An elevated risk for COVID-19 persisted even after controlling for nursing home residency in another study, exploring SARS-CoV-2 infection risk in individuals with dementia (Q. Wang et al., 2021). This raises interest in behavioral and biological rationale underlying risks associated with dementia, such as impaired ability to comply with prevention measures and impaired function of adaptive immunity in patients with dementia (Lutshumba et al., 2021).

From a biological perspective, SARS-CoV-2-attributed comorbidities, such as cardiovascular, metabolic, and renal diseases, are characterized by chronic systemic inflammation and immune dysregulation, which impair the body's ability to shape an effective antiviral response. Patients with CKD often exhibit reduced innate and adaptive immune function, making them more susceptible to infections. Additionally, both CKD and CVD are linked to endothelial dysfunction and upregulation of ACE2 receptors – the primary entry point for SARS-CoV-2 – potentially facilitating viral entry into host cells (Shirbhate et al., 2021). From a behavioral standpoint, individuals with these chronic conditions typically require frequent contact with healthcare services, including in-hospital care, which may

potentially increase their exposure to infection and several outcomes. Thus, hospital-acquired SARS-CoV-2 infection was observed in up to 2% of all hospital admissions during the first year of the pandemic in England (Cooper et al., 2023). Moreover, a meta-analysis of 21 studies revealed that nosocomial COVID-19 cases had a 30% higher risk of death, and those older and frailer individuals were twice as likely to die due to hospital-acquired COVID-19 compared to their community-infected counterparts (Ponsford, 2022). Another study confirmed that the elevated risk of severe outcomes associated with nosocomial COVID-19 cases persisted during the Omicron phase of the pandemic. However, the magnitude of this risk was partially reduced (Klompas et al., 2024). There are no studies on hospital-acquired SARS-CoV-2 infections in Estonia.

Thus, while vaccination reduces the impact of comorbidities on the risk of primary infection, certain vulnerable groups among vaccinated individuals remain at elevated risk and may benefit from additional support, such as targeted counseling on infection prevention and timely access to booster doses.

6.2. Individual-level risk factors for severe COVID-19 in unvaccinated and vaccinated populations.

6.2.1 Overall hospitalization trends in Estonia

Hospitalization rates reached their peak during spring 2021 (see Methods, Fig. 3). The first observable decline in severe COVID-19 cases occurred during late spring and summer 2021, coinciding with the start of the mass-vaccination program in Estonia. Between late 2021 and early 2022, hospitalizations followed a dual-peaked pattern: the first, in autumn 2021, was driven by the Delta variant and likely influenced by seasonal factors; the second coincided with the rapid spread of the more transmissible Omicron variant, following a brief decline due to rising immunity (Genomics & Transcriptomics Data, s.a.). The stable flattening of hospitalization curves following was probably driven by a combination of lasting vaccine-induced and naturally acquired immunity, along with the reduced virulence of Omicron and its subvariants.

Although the two cohorts – unvaccinated individuals observed during the first year of the COVID-19 pandemic and vaccinated individuals monitored following the launch of Estonia's mass vaccination program – were part of separate studies with differing contexts, the data consistently indicate that there was a substantially lower incidence of severe COVID-19 cases among vaccinated individuals. These findings align with other analyses of the COVID-19 pandemic in Estonia, which consistently show lower hospitalization rates among vaccinated individuals across various stages of the pandemic, with a greater difference observed before Omicron became widespread (Fischer, n.d.).

The overall proportion of severe COVID-19 cases among vaccinated individuals during the circulation of one of the most virulent Delta SARS-CoV-2

variant (Bhakta et al., 2022; J. Liu et al., 2023) was more than six times lower (1,2% vs 8%) compared to the pre-vaccination era.

The notably low rate of severe COVID-19 cases among vaccinated individuals may be attributable to a combination of immunological, epidemiological, and behavioral factors, as in addition to vaccine-provided protection and herd immunity, vaccinated individuals might have a greater probability of interacting mainly with others who were also vaccinated or proven infection free through regular testing, especially during lockdowns and periods of strict public restrictions.

6.2.2 Impact of age and sex on COVID-19 severity in unvaccinated and vaccinated individuals

Age and sex consistently influenced the severity of COVID-19 in both vaccinated and unvaccinated groups, although vaccination significantly reduced the magnitude of this effect. In both groups, age is the most potent predictor of severe COVID-19. The risk of hospitalization, intensive care, and death increases progressively with each decade of life, demonstrating a definitive dose-response relationship in both the vaccinated and unvaccinated.

In the pre-vaccination era, children under 10 years old exhibited low rates of severe COVID-19 infection (below 2%). In contrast, hospitalization and death rates increased steadily with age, with 75% of hospitalized patients occurring in individuals over 50 years old. The period of low risk for severe infection in school-aged children is sometimes referred to as a 'honeymoon period,' thought to reflect a phase of optimal immune function (when the immune system is fully developed but not yet affected by age-related decline) and some age-related peculiarities of immune system function, such as enhanced cellular immunity and interferon production (R. Ahmed et al., 2007)**.** In contrast, older adults exhibit delayed and reduced interferon production: impaired type II interferon responses contribute to exaggerated inflammation and cytokine storm, while impaired type I interferon responses weaken early antiviral defenses and adaptive immunity (Feng et al., 2021). The age-related pattern of infection severity is consistently observed across many infectious diseases, including studies on COVID-19, polio, measles, HIV, MERS-CoV, and the 1918 influenza outbreak, where school-aged children typically experience the mildest forms of illness, while infants and adults suffer from more advanced disease (R. Ahmed et al., 2007; Choi et al., 2022; Glynn & Moss, 2020).

Our findings align with those from other studies, revealing an association of advanced age and higher risk for admission to the ICU and death from COVID-19 (Albtoosh et al., 2024; Taquet et al., 2022). In older individuals, breakthrough infections often present with milder symptoms and may lack fever as a primary indicator, which can lead to underestimation of disease severity and delays in appropriate clinical management. Combined with age-related immune decline, this can result in more severe outcomes (Albtoosh et al., 2024). Therefore, older vaccinated individuals should be carefully evaluated even when presenting with

mild symptoms, as severe cases and fatalities from BTI still occur in this age group.

Different mechanisms were proposed to explain vaccinated individuals' vulnerability, including autoantibodies against components of immunity (i.e., interferon-1), which may attenuate protection apart from vaccine-induced antibody response (Antolí et al., 2025), age-related immunosenescence contributing to lower vaccine-induced neutralizing antibody responses (Bai et al., 2022; Lustig et al., 2021), as well as chronic disease-related attenuated vaccine immunogenicity (Boroumand et al., 2022; Naruse et al., 2021). Besides that, younger individuals may exhibit stronger immunogenicity regarding mRNA vaccines, evidenced by higher neutralizing antibody levels and anti-S IgG titers, compared to older adults (Bachmann et al., 2025).

These insights may help explain the rare but severe outcomes observed in some vaccinated individuals. However, given that the at-risk population (those over 50 years old) comprises 40% of the total (Statistikaamet: statistika andmebaas, n.d.), these outcomes still represent a significant concern and warrant attention.

Being female also provides a significant protective effect against severe outcomes in both cohorts. While this protection is substantial in the unvaccinated, particularly against critical and lethal outcomes, female sex still plays a protective role against severe breakthrough infections. However, the overall crude incidence of severe disease is far lower. These findings align with those from other studies, where Males consistently exhibit a higher risk of severe COVID-19 and death compared to females, in both vaccinated and unvaccinated individuals, as well as in inpatient and outpatient settings (Agrawal et al., 2021; Booth et al., 2021; Galbadage et al., 2020; Pijls et al., 2021).

This disparity is attributed to a combination of biological, immunological, and behavioral factors. Biologically, males tend to have less robust innate and adaptive immune responses, which may result in delayed viral clearance and heightened inflammatory reactions. Testosterone has been shown to suppress immune function, while estrogen in females may enhance antiviral responses and modulate inflammation (S. L. Klein & Flanagan, 2016). Besides that, studies have revealed significant heterogeneity in the sex-related immunogenicity of COVID-19 vaccines, with some studies reporting lower T cell responses and faster antibody decline in males (Bachmann et al., 2025). Similar patterns were observed for other vaccines, such as influenza, measles, smallpox, hepatitis A and B, thus highlighting sex-specific disparities in protection levels against vaccine-preventable diseases (S. L. Klein et al., 2010; Wen et al., n.d.). The X chromosome plays a critical role in shaping sex-specific immune responses to a wide range of viral infections, including SARS-CoV-2. Females benefit from the dual expression of immune genes, resulting in skewed X-inactivation that favors the normal allele and stronger antiviral responses. At the same time, males are more susceptible to immune dysregulation if there is damage in the immune-regulating loci of their X chromosome (Libert et al., 2010).

Besides immunological differences in response to infections and vaccinations, several other factors increase the risk for men, including comorbid conditions and risk behaviors. Men are more likely to suffer from advanced cardiovascular diseases, which contribute significantly to deadly COVID-19 outcomes. Furthermore, certain risk factors – such as hyperlipidemia and obesity – are more strongly associated with fatal cardiovascular complications in males than in females, while increasing the negative impact of these highly prevalent diseases during COVID-19 (Prospective Studies Collaboration, 2007; Song et al., 2014). A study on adherence to COVID-19 restriction measures in Estonia found that males were less likely to follow the restrictions implemented to contain the spread of the virus. Ethnicity and language were not significant predictors (Tulviste et al., 2025).

6.2.3 Impact of comorbidities on the risk of severe COVID-19 in unvaccinated and vaccinated individuals

The role of comorbidities as contributors to severe COVID-19 outcomes was recognized early in the pandemic from studies performed on severely ill hospitalized patients (Du et al., 2021; Gerayeli et al., 2021; Kumar et al., 2021; C. Li et al., 2023; Williamson et al., 2020). We observed similar results in the unvaccinated cohort, with cardiovascular, liver, cerebrovascular, kidney, metabolic, pulmonary, and different immunocompromising states (i.e., cancer, AIDS) serving as major contributors to hospitalization with COVID-19 in both unvaccinated and vaccinated cohorts. Vaccinated individuals exhibited similar patterns, although the strength of association was attenuated in the vaccinated cohort, and lacked significance for some comorbidities, such as hypertension or obesity.

CKD was significantly associated with severe COVID-19 outcomes in both vaccinated and unvaccinated cohorts, aligning with other studies identifying it as a strong predictor of hospitalization and mortality (Y. Cheng et al., 2020; Lee et al., 2021; Smits et al., 2023; Williamson et al., 2020).

Patients with dementia were less likely to be admitted to hospital and intensive care units despite high mortality, which may reflect impaired access to appropriate medical management for people with dementia rather than a reduced risk of severe COVID-19 infection. These findings may reflect both biological and behavioral factors, as cognitive impairment can hinder symptom reporting and timely care, alongside possible immune alterations in Alzheimer's disease, leading to impaired development of adaptive immunity after vaccination and exaggerated immune response during infection (van der Willik et al., 2019). Comprehensive data from multiple studies confirm that patients with dementia face an increased risk of death following SARS-CoV-2 infection (N. Liu et al., 2020).

Even a moderate comorbidity burden (CCI score of 1–2) was associated with a twofold increase in hospitalization regardless of vaccination status, and individuals with a higher comorbidity burden (CCI $\geq$3) exhibited even greater risk. The prevalence of impaired kidney function was about ten times higher (11%

vs 1%), diabetes was roughly four times higher (28% vs 6-9%), and cerebrovascular diseases were nearly eight times higher (23% vs 3%) among severely ill patients in the vaccinated group compared to the unvaccinated. This disparity suggests that while vaccination substantially reduces the overall risk of severe COVID-19, its protective effect may be diminished in individuals with underlying conditions that compromise immune function or disrupt physiological pathways involving the renin-angiotensin system, which is directly targeted by SARS-CoV-2 through the ACE2 receptor. This finding aligns with other studies, which have identified CKD, diabetes, and cardiovascular diseases as major contributors to severe COVID-19 breakthrough infections, especially in the presence of other comorbidities (Bea et al., 2023; Smits et al., 2023).

Current evidence suggests that adequate protection against SARS-CoV-2 requires both arms of adaptive immunity – cellular and humoral responses. In patients with CKD, liver disease, advanced cardiovascular diseases, or diabetes, however, immune system alterations – particularly premature immunosenescence and persistent low-grade systemic inflammation – impair the generation of effective immune responses. These dysfunctions attenuate the development of protective immunity following both natural infection and vaccination, thereby highlighting the importance of timely boosters and additional protective measures (Babel et al., 2022; Lustig et al., 2021).

Although the studies on vaccinated and unvaccinated cohorts were conducted during different phases of the pandemic, characterized by the dominance of wild-type and Alpha variants from 2020 to early 2021 (unvaccinated cohort), and the Delta variant throughout 2021 (vaccinated cohort), this variation in circulating SARS-CoV-2 VOCs does not appear to significantly affect the observed associations with age and sex, as the results were consistently one-sided. Moreover, studies conducted during the prevalence of different SARS-CoV-2 VOCs have consistently identified a similar repertoire of risk factors for adverse outcomes among infected individuals, with no substantial differences between variants. Research indicates that conditions such as diabetes, cardiovascular disease, and obesity have remained strong predictors of severe COVID-19 across variants, including wild-type, Delta, and Omicron, although some variability is possible (Ideguchi et al., 2024; Kahn et al., 2022; Yamaguchi et al., 2024).

6.2.4 Distribution of age groups and comorbidities across COVID-19 severity stages

Our findings showed a notable difference in hospitalization rates between vaccinated and unvaccinated individuals, depending on their comorbidity burden as measured by the CCI score. Most severely ill individuals from the unvaccinated cohort had no preexisting comorbidities known to modify their mortality risk (CCI = 0). This trend was observed across all stages of COVID-19 severity (non-severe disease, hospitalization, critical care), except for lethal disease, where individuals without a history of significant comorbid conditions were below 50%. In contrast, most individuals in the vaccinated cohort who experienced severe

COVID-19 had at least one high-risk comorbid condition (CCI ≥ 1). This illustrates the "prevention paradox," where most cases of disease (in this case, severe COVID-19) originate from individuals at relatively low personal risk (Raza et al., 2018).

Although CKD, AIDS, peripheral vascular disease, and a history of myocardial infarction were strongly linked to severe COVID-19 outcomes in the pre-vaccination group, their overall impact on healthcare was relatively small due to their low prevalence in the general population. Thus, only 1% of individuals with kidney disease were among severely ill unvaccinated COVID-19 patients. At the same time, while hypertension posed only a modest additional risk, a total of 43% of hospitalized unvaccinated individuals had hypertension as a comorbidity. Thus, its overall contribution to healthcare systems' burden during the pandemic may be considered significant.

However, the broader impact of CKD on healthcare systems during the COVID-19 pandemic may be underestimated, as a significant proportion of cases likely remain undiagnosed within the general population (Tangri et al., 2023; Van den Wyngaert et al., 2022; Yamada et al., 2019). In Estonia, CKD screening – particularly for albuminuria – is limited to high-risk groups, such as patients with diabetes or advanced hypertension, rather than the general population (Rosenberg et al., 2023). As a result, a substantial number of individuals at high risk for severe COVID-19 (those with undiagnosed CKD) might have been misclassified as low risk.

Vaccination shifted the age profile of severe COVID-19 cases. Before vaccines were available, the majority of hospitalized patients were under 70, with 13% of ICU admissions occurring in patients under 50. In contrast, among vaccinated individuals who experienced severe breakthrough infections, the majority (73%) were aged 70 or older. This contrast highlights the real-world scenario during the early phase of the pandemic, when healthcare systems were overwhelmed by relatively young and otherwise healthy individuals. It also illustrates the evolving risk landscape in the mostly vaccinated population, where severe outcomes have become increasingly concentrated among older adults and those with substantial preexisting comorbidities.

While assessing individual risk for severe COVID-19 and the protective effect of vaccination is essential, it is equally important, especially in the context of a pandemic, to consider the total number of individuals requiring hospitalization and the factors that influence it. Understanding the absolute burden and the factors that influence it is essential for effective planning and resource allocation during public health emergencies.

6.2.5 The role of booster vaccination

The protective effect of the booster vaccine dose in our study was notable, reducing the risk of COVID-19-related hospitalization by 68%. This finding is in line with other studies that demonstrate enhanced innate and adaptive immunity after booster vaccinations, leading to improved vaccine-acquired protection

levels (G. Zhou et al., 2025). While advanced age was associated with a decline in antibody response after vaccination, booster doses were shown to mitigate this decline (Bachmann et al., 2025).

Numerous immunological mechanisms underlie the beneficial effects of booster vaccine doses. Thus, memory T cells play a key role in immune response formation by supporting antibody production. These cells remain inactive until they are re-exposed to their specific antigen, whether through infection or vaccination. After reactivation, they respond more rapidly and effectively than during the initial encounter, with faster expansion and longer persistence, resulting in a stronger and more durable response from prime-boost vaccination strategies (Mayer, L., 2024). In older people, booster-related additional protection is mainly related to B-cell responses (Kometani et al., 2024).

The benefits gained from boosting vaccination strategies are especially pronounced in the elderly population, as demonstrated in studies examining the effectiveness of booster vaccines against hospitalization and mortality across various age groups (Mallah et al., 2022; Park et al., 2024).

While studies on hybrid immunity show reduced COVID-19 associated risks in vaccinated individuals with prior SARS-CoV-2 infection (Agrawal et al., 2021), as well as diminished additional benefit from annual boosters in these individuals (Park et al., 2024), these findings should be interpreted with caution due to persistent individual risks associated with advanced age and underlying conditions (i.e., multimorbidity), as they continue to be linked to severe COVID-19 in the Omicron and post-Omicron era (Moreno Echevarria et al., 2024; Yamaguchi et al., 2024).

6.2.6 Time-dependent nature of vaccine-induced protection against breakthrough COVID-19

The risk of SARS-CoV-2 breakthrough infection began to increase two months after completing the primary vaccination course, while the protective impact of vaccination against severe outcomes persisted for up to six months. This finding aligns with studies exploring vaccine effectiveness during the same period (Tartof et al., 2021; Thomas et al., 2021). The interval between vaccination or revaccination and breakthrough COVID-19 has become progressively shorter in studies conducted during the widespread circulation of Omicron and its sublineages (Menegale F et al., 2023). Recent studies demonstrated that seasonal booster vaccines were effective in preventing symptomatic COVID-19 in approximately one-third of individuals aged 60 and older, though vaccine effectiveness declined significantly within three months (Laniece Delaunay et al., 2024).

Persistent viral mutations, along with changing individual-level risk factors like comorbidity burden, aging, and a range of other factors contributing to immunosenescence, should be monitored and considered when planning personalized protection strategies. From a future perspective, research on biological aging markers could be crucial in identifying individuals at higher risk for weaker innate and adaptive immune responses and severe outcomes in infectious diseases,

including COVID-19, thereby allowing for more personalized prevention strategies such as vaccination and targeted therapies (Tao et al., 2024).

Although all COVID-19 vaccines are designed to elicit neutralizing antibodies against the spike protein, their immunogenicity may vary depending on the form, structural configuration, and cellular context in which the antigen is presented (Heinz & Stiasny, 2021; L. Liu et al., 2020). As the spike protein is structurally unstable and prone to cleavage into subunits by human proteases, using the original, unstabilized version of the spike protein (i.e, ChAdOx1 nCoV-19 vaccine) may lead to weakened immunological response (Chaudhary et al., 2021; Corbett et al., 2020; Watanabe et al., 2021). Therefore, the type of vaccine administered may influence both the risk and timing of breakthrough infections. A sensitivity analysis of primary vaccination strategies implemented in Estonia (incl. viral vector, mRNA, and heterologous combinations) revealed differences in BTI and severe BTI incidence rates. Individuals vaccinated exclusively with viral vector vaccines exhibited a higher incidence of both outcomes compared to those receiving mRNA-based or mixed regimens (See Study II, Supplementary information 3)

These insights underscore the necessity for adaptable public health strategies that evolve continuously throughout a pandemic. Protective measures should respond to current epidemiological challenges, such as the high representation of young and healthy individuals among severely ill patients at a time when herd immunity is absent or just emerging. In later stages, when natural or vaccine-induced immunity is more widespread, older and high-risk individuals remain particularly vulnerable, emphasizing the importance of prioritizing them for enhanced surveillance and tailored prevention measures.

6.3 The effects of pre-COVID-19 vaccination on major acute cardiovascular events and mortality

Based on Estonian data, increased mortality persists for at least one year after COVID-19. Moreover, this increased risk is driven by cardiovascular death causes (Uusküla, Jürgenson, et al., 2022).

We investigated how vaccination prior to SARS-CoV-2 infection influences the risk of death and adverse cardiovascular events, aiming to understand its role in shaping post-infection outcomes. Special attention was given to how these risks change over time, emphasizing the time-sensitive nature of vaccine effectiveness. The study was conducted during 2021 and 2022, a period marked by a shift in predominant SARS-CoV-2 variants – from Delta in 2021 to Omicron in early 2022**.** As the study progressed, the proportion of vaccinated individuals in the population increased, coinciding with advancements in COVID-19 treatment and the emergence of the less pathogenic Omicron variant, which likely reduced the risk of acute complications and may have introduced additional bias. Although participants enrolled later, during the period when Omicron was the dominant variant, had slightly shorter follow-up time, they represented only a

small fraction of the cohort, and the incidence of primary outcomes in this subgroup was similar to that of the overall study population. While these temporal changes may have introduced some bias, the direction and magnitude of such bias remain uncertain.

The protective effect of vaccination against death and severe cardiovascular outcomes in our study lasted about three months after infection. The protective effect against death remained consistent across sex and age groups. Among people over 70, the total death rate after COVID-19 was, on average, twice as high for men as for women, while less notable sex-related differences were observed for MACE rates (see Study III, Supplementary file, Fig. 1A). Post-COVID-19 death rates were twice as high in the unvaccinated group as in the vaccinated, though this difference was less pronounced in younger participants. Notably, vaccinated women had the lowest observed mortality, suggesting a potentially stronger protective effect of vaccination in this subgroup. The protective effect of vaccination against long-term mortality was also evident in individuals who experienced non-severe COVID-19, indicating that long-term complications are not solely dependent on the severity of the initial infection.

Although vaccination was associated with a lower overall MACE risk, there were some age- and sex-related peculiarities, highlighting a possible short-term and transient increase in MACE incidence among older vaccinated men during the first three months after infection. This sex-related inconsistency in the protective effects of vaccination against acute cardio- and cerebrovascular events could stem from various factors, such as survivorship bias, unmeasured confounding factors (e.g., silent atherosclerosis (Bergström et al., 2021) or unstable arterial plaques in males (de Bakker et al., 2020) (Ruijter et al., 2015)), or sex- and age-related differences in virus-induced immune response.

Our previous analysis revealed that only individuals with significantly greater comorbidity burden, as defined by a CCI of 3 or higher, had an increased risk for breakthrough infection (See Study II, Table 2). Moreover, there were considerably more individuals with CCI of 3 or higher (23% vs 3%), individuals with diabetes (28% vs 6%), or kidney disease (11% vs 1%) among individuals with severe BTI in comparison to the historical unvaccinated cohort. Thus, when assessing the impact of vaccination on post-COVID-19 MACE rates, it is essential to recognize that these outcomes may specifically apply to a distinct subgroup – individuals who were vulnerable enough to contract the infection despite being vaccinated. As the vaccination policy targeted more vulnerable individuals with multiple risk factors, this population may inherently have a higher baseline medical risk. This elevated risk may be attributed to a higher prevalence of unmeasured or hidden risk factors associated with their primary diagnoses, which we could not adjust for. This, in turn, may indicate a possible underestimation of the actual vaccination effect in this highly vulnerable population.

In elderly patients, especially males, an ACE2/angiotensin imbalance, pre-existing comorbidities, combined with immunosenescence, worsen cardiovascular vulnerability and may contribute to a dysregulated or exaggerated immune

response when triggered by SARS-CoV-2 infection, even in previously vaccinated individuals**.** Immune activation triggered by infection in a vaccine-primed but altered immune system – combined with post-COVID-19 vascular endothelial damage – may unintentionally contribute to increased cardiovascular stress and adverse outcomes in individuals who survived COVID-19 due to vaccine-induced humoral protection. Thus, it was revealed in a retrospective cohort study that a history of SARS-CoV-2 breakthrough infection or vaccination after primary infection was associated with a higher likelihood of developing severe heart failure or cardiogenic shock following an acute myocardial infarction. This finding may be attributed to an enhanced immune response resulting from hybrid immunity or unmeasured confounding factors (Blasco et al., 2024).

Notably, only 41% of MACE events occurred within the first three months after COVID-19, with a median time to event of four months. This suggests that cardiovascular complications after COVID-19 often emerge with a delay in individuals who survive the acute phase of infection and manifest weeks after infection rather than immediately. Thus, if vaccination primarily protects against acute-phase complications, increased vigilance should be maintained for delayed-onset cardiovascular events regardless of vaccination status, especially in high-risk populations like older males.

COVID-19 is not the only infection related to adverse cardiovascular outcomes. Infections such as influenza, *Streptococcus pneumoniae*, and respiratory syncytial virus (RSV) are known to exacerbate heart failure, increase the risk of acute cardiovascular events – with myocardial infarction risk rising up to sixfold after influenza – and significantly worsen outcomes in patients hospitalized for myocardial infarction (Brown et al., 2015; Kwong et al., 2018; Penders et al., 2025; Rus et al., 2024; Warren-Gash et al., 2018). If vaccination preserves the lives of the most vulnerable individuals, a delayed infection-driven vascular injury (Aljadah et al., 2024), combined with pre-existing vulnerability, could contribute to the observed increase in MACE incidence in the vaccinated group during a short period after infection. Further investigation may be warranted to elucidate this effect more thoroughly, with particular focus on sex-related differences.

COVID-19 poses a significant risk for those with underlying cardiovascular conditions. Given the strong protective effect of vaccination in reducing post-infection cardiovascular complications and mortality, it can be considered a primary prevention strategy against acute cardiovascular events, such as myocardial infarction or stroke. While vaccination improves survival in high-risk groups, some individuals remain vulnerable to post-acute COVID-19 sequelae. The cascade of cardiovascular events – potentially delayed by vaccination – highlights the need for increased clinical vigilance. Adjusting monitoring strategies, particularly in primary care settings, may be necessary to identify and manage these delayed complications of SARS-CoV-2 infection.

6.4 Strengths and limitations

A key strength of the studies discussed here lies in their use of large, population-based cohorts drawn from Estonia's national e-health databases. This approach ensures high generalizability, reliability, and statistical power. By leveraging real-world data, these studies provide valuable context that complements existing cohort research. Notably, the inclusion of individuals across the full spectrum of COVID-19 severity, including mild and asymptomatic cases confirmed by positive SARS-CoV-2 tests, enhances the representativeness of the findings.

The use of precise outcome definitions based on pre-existing research and high-quality data derived from reliable sources enabled accurate measurement of timing and risk factors, allowing for robust assessment of time-dependent effects of vaccination on outcomes such as breakthrough infections, MACE, and mortality. Advanced statistical techniques were employed to strengthen causal inference, particularly in the study of post-COVID-19 sequelae. TTE and IPT were used to adjust for confounding, with propensity scores derived from logistic regression models based on a minimally sufficient set of covariates identified through directed acyclic graphs.

To address potential bias from differential testing behavior, testing propensity was included as an adjustment factor in the analysis of breakthrough infections, accounting for variations in individual testing behavior and national testing policy over time.

Subgroup analyses revealed age- and sex-specific patterns in COVID-19 outcomes among vaccinated and unvaccinated individuals, offering nuanced insights into the association between vaccination and post-COVID-19 sequelae. The inclusion of fatal MACE cases as primary outcomes and death as a concurrent endpoint further strengthens the findings by diminishing survivorship bias.

However, several limitations arising from the retrospective study design must be acknowledged. Cohort studies are inherently prone to residual confounding from both suspected but unmeasured and unknown factors. None of the studies included behavioral determinants of health, such as smoking, alcohol use, social activity, occupational and familial exposure, poverty, compliance with treatment or containment strategies, which could influence exposure risk, disease severity, and long-term outcomes. Additionally, secondary health data lacked physical cardiometabolic parameters such as arterial stiffness, lipid profiles, kidney function, heart ejection fraction, and atherosclerotic plaque stability. All these factors could potentially contribute to disease severity and long-term outcomes.

Viral virulence, along with other external factors such as healthcare capacity and population immunity, may contribute to the severity of COVID-19 at the population level by interacting with individual vulnerabilities. Thus, the same individual-level risk factor, as age or gender, may potentially lead to different outcomes depending on the circulating SARS-CoV-2 strain or restriction measures implemented in a particular region. The three studies included in this dissertation were conducted during different phases of the pandemic, each

dominated by a distinct SARS-CoV-2 variant with known differences in virulence. Although the analyses were not adjusted for variant-specific effects, we recognize the necessity of interpreting the findings within the context of the dominant strain circulating when the participants were included. While individual-level risk factors remained relatively consistent across variants, their impact on severity may vary depending on the broader epidemiological and healthcare context. (Chapman et al., 2025; Y. Zhou et al., 2020).

Our study provides a valuable comparison of SARS-CoV-2 risk factors in two distinct populations, but it is important to acknowledge the limitations of this comparative approach. The primary limitation stems from the temporal separation and population differences between the two studies. The baseline population of the first study comprised unvaccinated, infection-naive individuals from the 2020-2021 period, while the second study was conducted in a population during a later phase of the pandemic. This temporal difference is significant, as it coincides with the emergence of new SARS-CoV-2 variants and shifts in population-level immunity, as well as evolving public health measures and social behaviors. While the narrative comparison provides valuable insights into how risk factors may have shifted, a direct causal inference is not possible due to these uncontrolled confounding factors.

The shared limitation for both studies is the reliance on laboratory-confirmed SARS-CoV-2 cases, which may not capture the actual burden of infection. Individuals with asymptomatic or mild infections who were not tested would not be included in either cohort. However, this limitation applies equally to both the unvaccinated and vaccinated groups and thus does not necessarily undermine the validity of the comparisons. The observed risk factors are representative of the tested population within each study's specific time frame. Despite this, the true effect size of the associations between risk factors and infection may be underestimated.

These limitations should be considered when interpreting our findings, but they do not diminish the relevance of the narrative comparison in highlighting a clear pattern of SARS-CoV-2 risk factors despite changing population-level immunity and viral evolution.

The impact of SARS-CoV-2 subvariants and vaccine types was not fully explored. In the study of post-COVID-19 MACE and mortality, most participants received mRNA vaccines, which helped reduce bias from vaccine heterogeneity. However, the breakthrough infection study could not fully explore the vaccine-specific effects due to the wide variety of vaccine combinations used, resulting in a loss of statistical power.

Another potential source of bias in the breakthrough infection study stems from psychological factors influencing testing behavior and national testing policy. Thus, vaccinated individuals in Estonia were not required to undergo regular testing for mild or asymptomatic infections, likely leading to an underestimation of mild cases in this group. Moreover, it is possible that vaccinated individuals were less likely to seek testing or medical attention in case of mild

infections, potentially due to a perceived sense of security associated with their vaccination status.

The small number of MACE cases among vaccinated individuals prevented a more detailed analysis by COVID-19 severity.

While administrative data provided a comprehensive and reliable source of information, potential biases may arise from coding practices, missing diagnostic codes due to poor compliance or prolonged absence from medical care, and systematic underdiagnosis of conditions such as dyslipidemia, obesity, and chronic kidney disease.

Early testing policies in Estonia initially prioritized older adults and individuals with specific comorbidities, which may have skewed early data toward more severe cases. However, by April 2020, testing eligibility was expanded to include all symptomatic individuals, and by July 2020, a universal testing strategy was introduced. This strategy provided free PCR testing to all residents, regardless of insurance status, health condition, or symptom severity. In addition, mass testing programs were implemented in healthcare and workplace settings to detect and prevent early local outbreaks of infection. Given that Estonia's testing rates exceeded the EU average at the first stages of the pandemic, this supports the reliability and completeness of the testing data used in the analyses. (OECD & European Observatory on Health Systems and Policies, 2021; Uusküla, Kalda, et al., 2022).

7. CONCLUSIONS

This dissertation, based on three population-based cohort studies in Estonia utilizing electronic health data, identifies vulnerable populations and reveals the changing nature of COVID-19 outcomes over time – findings that are crucial for the development of effective prevention and monitoring strategies. The analysis focused on SARS-CoV-2 infection and severe COVID-19 risk factors in unvaccinated and vaccinated populations, and the impact of vaccination on long-term COVID-19 sequelae.

The risk of infection was higher among females, working-age individuals, and those with comorbidities. Breakthrough infections were more common among those with comorbidities and lower levels of education. However, the role of sociodemographic factors in susceptibility to SARS-CoV-2 infection appears more complex, likely reflecting difficult-to-measure social and behavioral factors. The main risk factors for severe disease were increasing age and comorbidities. The risk increased with the number of underlying conditions, with chronic kidney disease showing the strongest association for severe COVID-19. Additionally, individuals with dementia may have experienced disparities in hospitalization and intensive care use. COVID-19 vaccination markedly attenuated the influence of age and comorbidities on disease severity and provided sustained protection against severe outcomes for at least six months. Booster vaccination provided significant additional protection against severe outcomes. Certain conditions, such as diabetes, liver disease, lung disease, cerebrovascular disease, and kidney disease, remained notable risk factors for severe COVID-19, even in vaccinated individuals. Vaccination provided substantial time-limited protection against major acute cardiovascular COVID-19 sequelae and mortality, with nuanced effects on age- and sex-related patterns.

The results of this study support the implementation of risk-based and scheduled prevention strategies, enhanced monitoring of vulnerable groups after COVID-19, and a broader role of vaccination as part of a long-term health protection strategy. Future efforts must address the evolving immunity landscape and sociodemographic factors, ensuring equitable access to care, particularly for vulnerable groups whose risk of severe disease and long-term complications may not be fully mitigated by vaccination alone. Enhanced post-infection monitoring and targeted interventions in vulnerable populations are crucial for reducing adverse outcomes in both vaccinated and unvaccinated individuals.

8. IMPLICATIONS FOR PRACTICE AND CONSIDERATIONS FOR FUTURE RESEARCH

Risk-stratified population-based prevention strategies
Although vaccination reduces the impact of several traditional risk factors, individuals of advanced age and those with multiple comorbidities still face a substantial risk of severe COVID-19. When planning preventive measures, such as vaccination or barrier protection, the risk associated with infection and disease severity should be continuously monitored, considering the changing landscape of population immunity, as well as several additional factors that may influence exposure and susceptibility. During the early stages of the pandemic, it is essential to consider the healthcare burden posed by individuals without conventional risk factors for severe outcomes. Further, public health and clinical strategies must be tailored to risk groups, acknowledging that even individuals who have received preventive care may still be at risk for severe outcomes.

Clinical tool development
Developing reliable, user-friendly, and comprehensive clinical tools for the early identification of high-risk populations may aid in risk stratification, particularly in primary care settings. These tools should be continuously refined, as the strength of associations changes with shifting immunity levels. Since vaccination status significantly modifies risk, it should be included in any predictive models or scoring systems.

Enhanced surveillance for vulnerable populations
Enhanced post-infection monitoring for health complications is critical for vulnerable subgroups, particularly older males who may experience delayed adverse events. As vaccination helps save lives, it is essential to account for the survivorship effect and the potentially greater prevalence of individuals with previously unattended risk factors contributing to post-COVID cardiovascular complications. This phenomenon highlights the need for in-depth investigation of risk factors beyond traditional ones that may help better define the vulnerable population.

Vaccination as a broader preventive tool
Since vaccination demonstrated a protective effect against MACE, including COVID-19 vaccination in preventive care strategies – especially in cardiovascular disease prevention – may help lower long-term mortality. Proactively managing risks associated with infection can help reduce the burden of long-term consequences and improve outcomes in aging populations.

Data-driven preparedness
To build a robust national health crisis strategy, it is essential to ensure broad access to reliable testing and transparent diagnostic and reporting systems. This,

in turn, enhances the ability to rapidly analyze real-world data and identify evolving risk patterns. Investing in a coherent, centralized platform for data collection and information exchange, along with supporting local studies that reflect regional policies and specific contexts, is crucial for navigating healthcare responses during a pandemic.

Tailoring communication to local and demographic context.
Sociodemographic factors play a key role in shaping vaccine coverage and adherence to containment methods and should be considered when designing public alerting strategies. Further analysis is necessary to understand these differences and identify the psychological and behavioral factors underlying them. These factors should also be integrated into models forecasting infection surges during a pandemic.

Equitable care
Though dementia poses a significant risk factor for infection and poor outcomes, access to enhanced clinical care may be limited for affected individuals. To address this disparity, people with cognitive impairment must receive special attention to ensure equitable access to testing, treatment, and appropriate clinical management.

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10. SUMMARY IN ESTONIAN

COVID-19 riskitegurid ja tagajärjed: vaktsineerimise mõju nakatumisele, haiguse raskusastmele ja tervisetulemitele

COVID-19 pandeemia avaldas sügavat mõju paljude riikide tervishoiusüsteemidele, majandusele ja ühiskonnale tervikuna. Kolme esimese aasta jooksul põhjustas COVID-19 Eestis üle 25 000 hospitaliseerimise ning enam kui 3000 COVID-19-ga seotud surma. Haiguse kiire levik ja raske kulg immuunnaiivses ühiskonnas, plahvatuslikult kasvanud haiglate koormus ning hirm ja ebakindlus seoses uue terviseohuga sundisid rakendama ulatuslikke ja kiireloomulisi meetmeid viiruse leviku piiramiseks. Kõrgeim COVID-19-ga seotud suremus registreeriti Eestis 2021. aastal, mil haigus tõusis surmapõhjuste seas kolmandale kohale südame-veresoonkonna haiguste ja vähi järele.

Varased kohortuuringud, mis keskendusid peamiselt haiglapopulatsioonidele, kirjeldasid COVID-19 mitmetahulist kliinilist avaldumist ning rasket haiguskulgu, mis oli seotud mitmete kaasuvate krooniliste haigustega. Peagi sai selgeks, et COVID-19 ei piirdu üksnes hingamisteede haaratusega, vaid mõjutab mitmeid organsüsteeme, põhjustades potentsiaalselt eluohtlikke tüsistusi ja pikaajalisi tervisemõjusid läbi immuunsüsteemi häirunud regulatsiooni ning viiruse poolt käivitatud keerukate patofüsioloogiliste protsesside. COVID-19 läbipõdemist on seostatud nii kardiovaskulaarhaiguste esmashaigestumise sagenemise kui ka olemasolevate krooniliste haiguste ebasoodsa kuluga.

Vaktsineerimine kujunes keskseks strateegiaks raske COVID-19 ennetamisel, kuigi ei kõrvaldanud riski täielikult. Pandeemia edenedes ning SARS-CoV-2 spetsiifilise immuunsuse kujunedes suurel osal elanikkonnast – kas haiguse läbipõdemise või vaktsineerimise teel – muutus järjest olulisemaks haavatavate populatsioonide täpne määratlemine, et võimaldada tõenduspõhiste ja personaliseeritud ennetusstrateegiate väljatöötamist, tuginedes suuremahulistele populatsioonipõhistele andmestikele. Vaktsineerimise pikaajaline mõju COVID-19 järgselt ilmnevatele tervisemõjudele on samuti jätkuvalt oluliseks uurimisvaldkonnaks.

Uuringu eesmärgid

Käesoleva uuringu eesmärgiks oli uurida individuaalseid riskitegureid SARS-CoV-2 nakkuse ja raske COVID-19 haiguse kujunemisel ning hinnata COVID-19 vaktsineerimise pikaajalist mõju suurematele kardiovaskulaarsetele sündmustele ja pikaajalisele suremusele nakkuse järel. Alaeesmärkideks olid:

1. Tuvastada individuaalsed riskitegurid SARS-CoV-2 esmaseks nakatumiseks vaktsineeritud ja vaktsineerimata inimestel (Uuringud I–II).
2. Tuvastada raske COVID-19 kulu riskitegureid vaktsineeritud ja vaktsineerimata inimestel (Uuringud I–II).

3. Hinnata COVID-19-eelse vaktsineerimise mõju ägedatele kardiovaskulaarsetele sündmustele (ingl. *MACE, major acute cardiovascular event*) ja suremusele pärast COVID-19 (Uuring III).

Metoodika

Käesolevas uuringus kasutati kolme eraldiseisvat, kuid metoodiliselt sarnast retrospektiivset kohortuuringut, mis tuginesid Eesti riiklikele elektroonilistele terviseandmebaasidele.

- **Uuring I** keskendus SARS-CoV-2 ja raske COVID-19 riskifaktorite tuvastamisele isikutel, kellel puudus immuunsus SARS-CoV-2 viiruse vastu. Uuringusse kaasati 66 295 SARS-CoV-2-ga nakatunud isikut ja 254 958 kontrollisikut. Seoste hindamiseks kasutati andmeid uuritavate sotsiodemograafilise tausta ning kaasuvate haiguste kohta. Tervisliku seisundi hindamiseks kasutati Charlsoni komorbiidsusindeksit (CCI), mis arvutab koondskoori vastavalt esinevatele kaasuvatele haigustele ja nende seosele surmariskiga.
- **Uuring II** keskendus vaktsineeritud populatsioonile, et hinnata SARS-CoV-2 läbimurdeinfektsioonide riski ja raskusastet, ning nende muutust ajas. Uuringusse kaasati 184 132 inimest, kes olid saanud esmase COVID-19 vaktsiinikuuri ja kes polnud COVID-19 varem põdenud. Seosehinnangute leidmiseks kasutati andmeid uuritavate sotsiodemograafilise tausta ning kaasuvate haiguste kohta (nii CCI kui ja ka eraldiseisvate haiguste diagnoosikoodid)
- **Uuring III** hindas COVID-19-vastase vaktsineerimise mõju ägedatele kardiovaskulaarsetele sündmustele (infarkt, insult) ja üldsuremusele pärast nakatumist SARS-CoV-2-ga. Uuring hõlmas 33 554 inimest, kes olid nakatunud SARS-CoV-2-ga ajavahemikus aprill 2021 – mai 2022. Põhjusliku seose tuvastamiseks kasutati sihtkatse emulatsiooni (*ingl*. target trial emulation) kavandit. Uuritavate kohortide tasakaalustamiseks on kasutatud andmeid sotsiodemograafilise tausta ning kaasuvate haiguste kohta.

Tulemused

Pandeemia esimesel aastal SARS-CoV-2-sse nakatunute keskmine vanus oli 44,1 aastat ning enamik neist (76,5%) olid alla 60-aastased. SARS-CoV-2 nakkusrisk oli veidi kõrgem naistel võrreldes meestega (aOR 1,10; 95% CI 1,08–1,12) ning madalam lastel (<9 a; aOR 0,34; 95% CI 0,32–0,35) ja vanemaealistel (70–79 a; aOR 0,61; 95% CI 0,59–0,64) võrreldes 30–39-aastaste isikutega. Mitme kaasuva haiguse esinemine (Charlsoni komorbiidsuse indeks, CCI ≥3) suurendas nakkuseriski märgatavalt. Eraldiseisvatest diagnoosidest näitasid tugevat seost nakkuse riskiga dementsus, neeruhaigus ja ajuveresoonkonna haigused. COVID-19 kulg oli nakatunute seas valdavalt kerge. Samas vajas 6,5% nakatunutest haiglaravi ning 1,5% suri 30 päeva jooksul pärast haigestumist. Vanus oli tugevaim raske COVID-19 kulu ennustaja: iga 10 eluaasta lisandumine suurendas hospitaliseerimise riski 68%, intensiivravi vajadust 97% ning surmariski ligi neli korda. Üle 80-aastaste raske COVID-19 kulu risk oli tõusnud 16 korda (aRRR

16,55, 95%CI 14,69 – 18.65) võrreldes alla 50-aastaste uuritavatega.! Naissool oli raske haiguskulu suhtes oluline kaitsev mõju: naiste risk hospitaliseerimiseks oli 16% väiksem, intensiivravi vajadus 56% väiksem ning surmarisk 59% väiksem võrreldes meestega. Suurema kaasuvate haiguste arvuga (CCI skoor ≥3) inimestel kolmekordistus raske COVID-19 kulu risk ja neljakordistus surma risk. Mitmed kaasuvad haigused olid tugevalt seotud raske COVID-19 kuluga, nende seas kroonilise neeruhaigus demonstreeris tugevaima seose, suurendades hospitaliseerimisriski viis korda (aRRR 5,41; 95% CI 3,59–8,13) ning intensiivravi riski peaaegu kaheksa korda (aRRR 7,71; 95% CI 4,71–12,62). Ajuveresoonkonna haigused, südamehaigused, diabeet, rasvumine, uneapnoe, hüpertensioon, hüperlipideemia, pahaloomulised kasvajad ja maksahaigused olid seotud COVID-19 väga raske kuluga (intensiivravi vajadus). Dementsusega inimestel risk sattuda intensiivraviosakonda COVID-19 tõttu oli 62% vähem võrreldes nendega, kel puudus dementsuse diagnoos, samas nende inimeste risk surra COVID-19-sse oli 85% kõrgem. **(I uuring)**

Vaktsineeritud populatsioonis esines 29 688 läbimurdeinfektsiooni (16% vaktsineeritutest). Läbimurdeinfektsioonidega isikute keskmine vanus oli 48,9 aastat ning enamikul neist (84,7%) ei olnud olulisi kaasnevaid haigusi (CCI = 0). Nakatumisrisk oli kõrgem naistel võrreldes meestega (aHR 1,12; 95% CI 1,09–1,15) ning madalam vanemaealistel: 70–79-aastastel oli risk 66% väiksem ja ≥80-aastastel 69% väiksem võrreldes <40-aastastega. Keskmine ja kõrge haridustase olid seotud väiksema nakatumise riskiga vaktsineeritud isikutel võrreldes madalama haridustasemega. Läbimurdeinfektsioone esines harvemini tõhustusdoosi saanute seas (6% vs 25% esmase immuniseerimiskuuri läbinutel), kuigi kohandatud analüüs näitas, et tõhustusdoosi lisakaitse läbimurdeinfektsiooni eest oli pigem tagasihoidlik (aHR 0,95; 95% CI 0,90–0,99). Raske COVID-19 ning sellest tulenev haiglaravi vajadus kujunes 355 inimesel (1,2 % nakatanud vaktsineeritud isikutest). Hospitaliseerimisrisk suurenes vanusega: üle 80-aastastel oli see risk üle seitsme korra kõrgem võrreldes alla 40-aastastega. Naissool oli kaitsev mõju raske läbimurdeinfektsiooni eest (aHR 0,68, 95%CI 0,55–0,84). Kõrgem kaasuvate haiguste arv suurendas COVID-19 raske kulu riski vaktsineeritud isikutel ning üksikdiagnoosidest näitasid tugevaima seose maksahaigused (aHR 2,00; 95% CI 1,11–3,61), neeruhaigused (aHR 1,92; 95% CI 1,32–2,80), ajuveresoonkonna haigused (aHR 1,72; 95% CI 1,11–2,67), kopsuhaigused (aHR 1,72; 95% CI 1,28–2,31) ja diabeet (aHR 1,71; 95% CI 1,29–2,27). Hüpertensioon ja rasvumine ei olnud seotud raskema COVID-19 kuluga vaktsineeritud isikutel. Vaktsineerimisest saadud kaitse raske COVID-19 kulu eest püsis vähemalt kuus kuud ning vaktiini tõhustusdoos vähendas hospitaliseerimise riski veel 68% võrra (aHR 032, 95%CI 0,19 – 0,54). **(II uuring)**

Uuringus jälgiti ühe aasta jooksul kokku 18 223 isikut, kes olid vaktsineeritud enne esmakordset nakatumist SARS-CoV-2-ga, ning 15 331 vaktsineerimata isikut. Ühe aasta jooksul pärast esmakordset SARS-CoV-2 nakatumist esines kokku 321 MACE juhtumit: 170 vaktsineeritutel (0,9%) ja 151 vaktsineerimata isikutel (1,0%). Mediaanaeg MACE-sündmuseni oli 123 päeva ning enamik neist (59%) toimus rohkem kui kolm kuud pärast infektsiooni. MACE risk jälgimis-

perioodi lõpuks oli 29% madalam vaktsineeritud isikutel (wIRR 0,71; 95% CI 0,58–0,84) ning suurim vahe vaktsineeritud ja vaktsineerimata isikute vahel MACE-i esmashaigestumise osas oli jälgitav esimese kolme kuu jooksul pärast nakatumist. Alagruppide analüüs näitas suurimat efekti vaktsineeritud naistel ning efekti puudumist üle 70-aastastel vaktsineeritud meestel koos lühiajalise MACE sageduse tõusuga selles rühmas. Surmasid esines kokku 640 juhul: 253 vaktsineeritutel (1,4%) ja 387 vaktsineerimata isikutel (2,5%). Enamik surmajuhtumeid (60%) toimus esimese kolme kuu jooksul pärast nakatumist; mediaanaeg surmani oli 53 päeva. Vaktsineeritud isikutel oli suremus 68% madalam võrreldes vaktsineerimata inimestega (wIRR 0,32; 95% CI 0,28–0,36) ning vaktsineerimise kaitsev mõju oli tugevaim alla 70-aastastel naistel ((wIRR 0.18; 95%CI 0.09 - 0.27) ja üle 70-aastastel meestel (wIRR 0,31; 95% CI 0,24–0,39). Vaktsiini kaitsev mõju COVID-19 järgse surma eest oli tugevamini väljendunud esimese kolme kuu jooksul, olles märgatav ka kerge- ja mõõduka COVID-19 raskusastmega inimestel. **(III uuring)**

Kokkuvõte

Käesoleva uurimistöö tulemused, mis põhinevad kolmel Eesti rahvastikupõhisel kohortuuringul, toovad esile haavatavad populatsioonid ja COVID-19 tagajärgede ajas muutuvat iseloomu, mis on oluline ennetus- ja jälgimisstrateegiate kavandamisel. Uurimistöös analüüsiti SARS-CoV-2 nakkuse ja raske COVID-19 kulgemise riskitegureid ning vaktsineerimise mõju haiguse pikaajalistele tagajärgedele, tuginedes Eesti elektroonilistele populatsioonipõhistele andmebaasidele. Leiti, et nakatumise risk oli kõrgem naistel ja tööealistel isikutel. Sotsiodemograafiliste tegurite täpne mõju SARS-CoV-2 nakkusele ja haiguse raskusastmele jääb siiski raskesti hinnatavaks, olles mõjutatud mitmete keerukate ja sageli halvasti mõõdetavate käitumuslike ja sotsiaal-psühholoogiliste tegurite poolt.

Haiguse raske kulu peamised riskitegurid nii vaktsineerimata kui ka vaktsineeritud isikutel olid kõrgem vanus ja suurem hulk kaasuvaid haigusi. Mõnede haiguste jaoks, nagu diabeet, südamehaigused, vähk, kopsuhaigused, peaaju veresoonte haigused ja neeruhaigused, püsis suurem risk ka pärast vaktsineerimist, kuigi vaktsineerimine leevendas nende tegurite mõju ulatust ning mõned haigused ei olnud enam seotud raskema COVID-19 kuluga. Kroonilise neeruhaiguse olemasolu seostus kõige tugevamalt raske COVID-19 kuluga nii vaktsineerimata kui ka vaktsineeritud inimestel. Võrreldes teiste krooniliste haigustega, hospitaliseeriti dementsusega inimesi harvem ning nende intensiivravi saamise tõenäosus oli väiksem, kuigi dementsuse diagnoos tõstis oluliselt COVID-19-ga seotud surma riski.

Kuigi läbimurdeinfektsioonid olid sagedased, vaktsineerimise kaitsev mõju haiguse raske kulu vastu kestis vähemalt kuus kuud ning vaktsiini tõhustusdoos andis olulise lisakaitse. COVID-19 vastane vaktsineerimine omas kaitset ägedate kardiovaskulaarsete sündmuste ja surma eest pärast COVID-19 põdemist. See kaitsev toime oli ajaliselt piiratud ja varieerus vastavalt vanusele ja soole.

Käesoleva töö tulemused toetavad riskipõhiste ja ajastatud ennetusstrateegiate rakendamist, tõhustatud järelevalvet haavatavates rühmades COVID-19 põdemise järel ning vaktsineerimise käsitlemist laiemalt kui ainult nakkuse ja raske haiguse kulu ennetamise vahendit. Ennetusstrateegiate kujundamisel tuleb arvestada haavatavate rühmadega, kelle risk raskeks COVID-19 kuluks ja tõsisteks tagajärgedeks ei pruugi olla vaktsineerimisega täielikult maandatav. Riskipõhised lähenemised peavad lähtuma elanikkonna muutuvast immuunsusest, arvestama sotsiodemograafiliste teguritega ning tagama võrdse ligipääsu ravile.

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As with any research, especially observational studies, the quality of the data and the dedication of those responsible for its collection and processing are crucial. Therefore, I first extend my deepest gratitude to all frontline workers, registrars, and those who guided healthcare during the most challenging and uncertain early years of the COVID-19 pandemic. Your courage, self-sacrifice, and resilience saved lives and made this data-driven analysis possible.

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I would also like to extend my sincere gratitude to my team at the family medicine practice – my nurses and fellow physicians. Your patience, collegiality, and unwavering readiness to adapt to rapidly changing circumstances have been invaluable. Together, we have walked through fire and water, and your support has made it possible to continue providing care while pursuing this research.

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12. PUBLICATIONS

13. CURRICULUM VITAE

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Education

2021–present	University of Tartu, Faculty of Medicine, Doctoral Studies
2009–2014	University of Tartu, General Practitioner Residency
2002–2009	University of Tartu, Faculty of Medicine, Medical Studies
1996–2002	Narva Pähklimäe Gymnasium

Work experience

2022–present	Family Physician and Head of Family Medical Centre, OÜ Dr. Meister, Tartu, Estonia
2017–present	Junior Research Fellow in Family Medicine, Department of Family Medicine, Institute of Family Medicine and Public Health, University of Tartu
2021	Physician, Department of Inpatient Nursing, Elva Hospital
2018–2023	Guidelines Methodology Advisor, Cener for Evidence Based Practice, University of Tartu
2017–2021	Expert, Estonian Unemployment Insurance Fund
2010–2017	Family Physician, OÜ Dr. Monika Vask
2015–2017	Physician, Emergency Department, Viljandi Hospital
2013–2016	Physician, Tartu Ambulance
2005–2009	Nurse, Children's Clinic, Tartu University Hospital
2004–2005	Attendant, Neurology Clinic, Tartu University Hospital

Projects and Research

2013–2014 Chlamydia Testing Training in Europe (CATTE) – project participant and trainer

2021–2023 Preparation of treatment guidelines and methodological advice:
- Prevention and treatment of bedsores, Estonian Health Insurance Fund, 2023
- Smoking cessation counseling, Estonian Health Insurance Fund, 2022
- Treatment of chronic heart failure in primary care, Estonian Health Insurance Fund, 2021
- Rehabilitation of COPD patients, Estonian Health Insurance Fund, 2021
- Treatment of COPD, Estonian Health Insurance Fund, 2020
- Diagnosis and treatment of chronic venous insufficiency, Estonian Health Insurance Fund, 2019

2020–2023	COVID-19 disease case analysis and identification of risk groups in Estonia (CORIVA) – Project Manager
2024–present	Primary Health Care data on COVID-19 Pandemic in Europe (EURODATA) – project participant
2005–present	Study on ’Secondary Victim in Estonian Healthcare’ – project participant

Membership in Organizations
Estonian Society of Family Doctors (since 2014)
Estonian Medical Association (since 2016)
European General Practice Research Network (since 2024)

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2021–praegu	Tartu Ülikool, meditsiiniteaduste valdkond, doktorantuur
2009–2014	Tartu Ülikool, perearstiteaduse residentuur
2002–2009	Tartu Ülikool, arstiteaduskond, arstiõpe
1996–2002	Narva Pähklimäe Gümnaasium

Töökogemus

2022–praegu	perearst ja perearstikeskuse juhataja, OÜ Dr. Meister, Tartu Tervisekeskus
2017–praegu	nooremteadur, peremeditsiini õppetool, peremeditsiini- ja rahvatervishoiu instituut, Tartu Ülikool
2021	üldarst, statsionaarse õendusabi osakond, Elva Haigla
2018–2023	ravijuhendite metoodikanõunik, Ravijuhendite püsisekretariaat, Tartu Ülikool
2017–2021	ekspertarst, Eesti Töötukassa
2010–2017	perearst, OÜ Dr. Monika Vask
2015–2017	arst, erakorralise meditsiini osakond, Viljandi Haigla
2013–2016	arst, Tartu Kiirabi
2005–2009	meditsiiniõde, Lastekliinik, Tartu Ülikooli Kliinikum
2004–2005	hooldustöötaja, Närvikliinik, Tartu Ülikooli Kliinikum

Projektid ja teadustöö

2013–2014	Chlamydia Testing Training in Europe (CATTE) – projekti osaline ja koolitaja
2021–2023	Ravijuhendite koostamine ja meeskondade nõustamine: – Lamatishaavandite ennetus ja ravi, Eesti Haigekassa, 2023 – Suitsetamisest loobumise nõustamine, Eesti Haigekassa, 2022 – Kroonilise südamepuudulikkuse käsitlus esmatasandil, Eesti Haigekassa, 2021 – Kroonilise obstruktiivse kopsuhaigusega patsiendi taastusravi, Eesti Haigekassa, 2021 – Kroonilise obstruktiivse kopsuhaigusega patsiendi käsitlus, Eesti Haigekassa, 2020 – Jala veenilaiendite ja kroonilise venoosse puudulikkuse diagnoosimine ning ravi, Eesti Haigekassa, 2019
2020–2023	COVID-19 haigusjuhtumite analüüs ja riskirühmade väljaselgitamine Eestis (CORIVA) – projektijuht

2024–praegu Primary Health Care data on COVID-19 Pandemic in Europe (EURODATA) – projekti osaline
2005–praegu Uuring „Teisene kannatanu Eesti tervishoius“ – projekti osaline

Kuulumine organisatsioonidesse
Eesti Perearstide Selts (alates 2014)
Eesti Arstide Liit (alates 2016)
European General Practice Research Network (alates 2024)

DISSERTATIONES MEDICINAE UNIVERSITATIS TARTUENSIS

1. **Heidi-Ingrid Maaroos**. The natural course of gastric ulcer in connection with chronic gastritis and *Helicobacter pylori*. Tartu, 1991.
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8. **Ruth Mikelsaar**. Etiological factors of diseases in genetically consulted children and newborn screening: dissertation for the commencement of the degree of doctor of medical sciences. Tartu, 1993.
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