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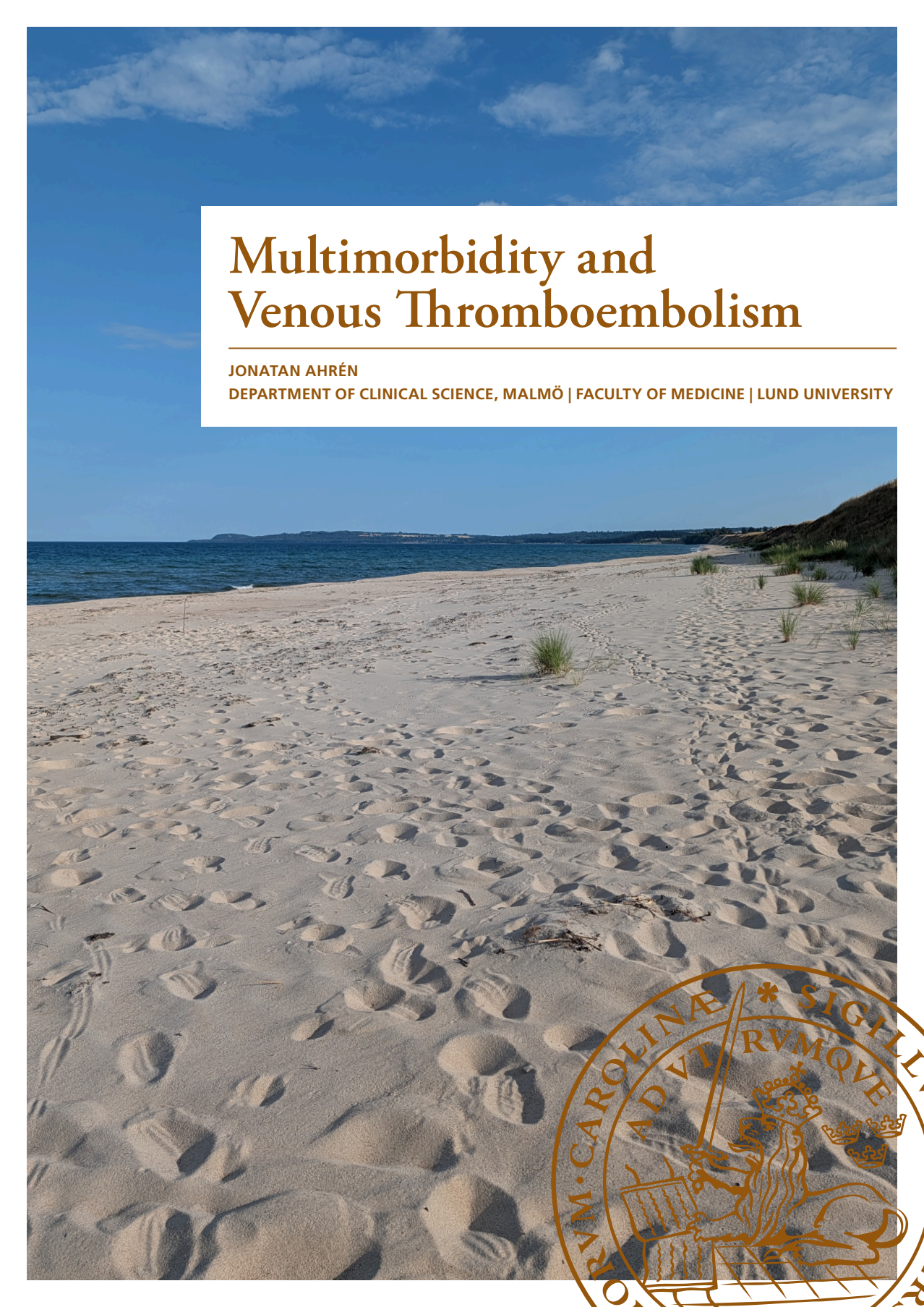
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Multimorbidity and Venous Thromboembolism

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Multimorbidity and Venous Thromboembolism

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Jonatan Ahrén



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DOCTORAL DISSERTATION

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Faculty opponent

Bledar Daka, Professor, District Medical Officer, School of Public Health and Community Medicine, Institute of Medicine, Sahlgrenska Academy at University of Gothenburg, Gothenburg

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Abstract:

Background: Venous thromboembolism (VTE) is the third most common cardiovascular disease and is associated with significant morbidity and mortality. The prevalence of multimorbidity, defined as the coexistence of two or more chronic conditions, is increasing globally, posing a major challenge for healthcare systems. While individual risk factors for VTE are well-known, the association between multimorbidity and VTE has not been previously explored.

Aims: The aim was to investigate any association between multimorbidity, its severity (number of diagnoses), and specific disease clusters with the risk of VTE, and to evaluate multimorbidity as a predictor of incident VTE.

Methods: The studies were based on Swedish national data, the National Patient Register, the Multigeneration Register, the Total Population Register, the Swedish Cause of Death Register, and primary care data. Multimorbidity was defined using a list of 45 noncommunicable diseases. Statistical analyses included cross-sectional studies and cohort studies using landmark analysis to calculate odds ratios (OR) and hazard ratios (HR). Principal component analysis was used to identify distinct disease clusters.

Results: The results demonstrate a strong, dose-graded association between multimorbidity and VTE. Individuals with multimorbidity had a VTE risk of OR 3.16 (95% CI: 3.06–3.27), with the risk increasing to an OR of 9.08 (95% CI: 8.56–9.64) for those with five or more diagnoses. Landmark analyses confirmed that multimorbidity is an independent predictor for incident VTE with an adjusted HR of 2.47 (95% CI: 2.24–2.72). Seven of the nine identified disease clusters, including cardiometabolic and psychiatric clusters, were significantly associated with VTE. Significant familial associations were observed, with risk estimates correlating to the degree of relatedness. Adjusted OR 1.89 (95% CI: 1.17–3.05) in twins and OR 1.07 (95% CI: 1.04–1.10) in cousins, indicating a weak shared familial association between multimorbidity and VTE, but it is the individually accumulated disease burden and acquired factors that are the main drivers rather than a genetic cause. Primary care data confirmed multimorbidity as an independent risk factor in a primary healthcare setting.

Conclusion: Multimorbidity is a novel, dose-graded risk factor and predictor for VTE. Incorporating the total disease burden and specific disease clusters into clinical assessments may improve VTE risk prediction.

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Multimorbidity and Venous Thromboembolism

Jonatan Ahrén



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MADE IN SWEDEN 

*This thesis is dedicated to my family
and to those who supported me along the way.*

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Abstract

Background: Venous thromboembolism (VTE) is the third most common cardiovascular disease and is associated with significant morbidity and mortality. The prevalence of multimorbidity, defined as the coexistence of two or more chronic conditions, is increasing globally, posing a major challenge for healthcare systems. While individual risk factors for VTE are well-known, the association between multimorbidity and VTE has not been previously explored.

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Results: The results demonstrate a strong, dose-graded association between multimorbidity and VTE. Individuals with multimorbidity had a VTE risk of OR 3.16 (95% CI: 3.06–3.27), with the risk increasing to an OR of 9.08 (95% CI: 8.56–9.64) for those with five or more diagnoses. Landmark analyses confirmed that multimorbidity is an independent predictor for incident VTE with an adjusted HR of 2.47 (95% CI: 2.24–2.72). Seven of the nine identified disease clusters, including cardiometabolic and psychiatric clusters, were significantly associated with VTE. Significant familial associations were observed, with risk estimates correlating to the degree of relatedness. Adjusted OR 1.89 (95% CI: 1.17–3.05) in twins and OR 1.07 (95% CI: 1.04–1.10) in cousins, indicating a weak shared familial association between multimorbidity and VTE, but it is the individually accumulated disease burden and acquired factors that are the main drivers rather than a genetic cause. Primary care data confirmed multimorbidity as an independent risk factor in a primary healthcare setting.

Conclusion: Multimorbidity is a novel, dose-graded risk factor and predictor for VTE. Incorporating the total disease burden and specific disease clusters into clinical assessments may improve VTE risk prediction.

Populärvetenskaplig sammanfattning

Multisjuklighet och risken för venös tromboembolism

I takt med att livslängden ökar och den medicinska utvecklingen går framåt lever befolkningen allt längre. Medicinska genombrott och förbättrade levnadsvillkor har gjort att många tidigare dödliga tillstånd nu är kroniska sjukdomar som kan behandlas under decennier. Denna framgång har medfört en ny utmaning för hälso- och sjukvården: fler blir multisjuka. Multisjuklighet, multimorbiditet, definieras vanligtvis som samexistensen av två eller flera kroniska sjukdomar hos en och samma individ. Trots att detta tillstånd blir allt vanligare, har den medicinska forskningen och kliniska praxisen länge varit fokuserad på en diagnos i taget. Denna avhandling syftar till att undersöka om multimorbiditeten påverkar risken att få venös tromboembolism (VTE).

Vad är VTE?

VTE är ett samlingsnamn för blodproppar i venerna. Två allvarliga tillstånd finns: djup ventrombos (blodpropp i de djupa venerna, oftast i benen) och lungemboli (blodpropp i lungan). VTE utgör den tredje vanligaste kardiovaskulära sjukdomen, efter hjärtinfarkt och stroke, med en årlig förekomst på cirka 1–3 fall per 1000 individer. Sjukdomen är förknippad med betydande lidande och dödlighet.

Symtomen vid VTE kan vara diffusa och svåra att tolka. En propp i benet kan ge smärta och svullnad som påminner om en enkel muskelsträckning, medan en propp i lungan kan yttra sig som hosta, andfåddhet eller bröstsmärta, symptom som kan misstolkas som en vanlig förkylning eller lunginflammation. Den kliniska osäkerheten gör det utmanande för läkare att avgöra vilka patienter som bör genomgå utredningar som skiktröntgen eller ultraljud. Att identifiera nya, mätbara riskfaktorer är därför av intresse. Syftet med denna avhandling var att se om multisjuklighet kan tänkas vara en sådan riskfaktor i framtiden.

De studier som ingår i denna avhandling baseras på svenska nationella registerdata samt Primärvårdsdata. Genom att sammanlänka data från Patientregistret, Dödsorsaksregistret, Flergenerationsregistret och Totalbefolkningens register samt även data från primärvården har det varit möjligt att studera miljontals individer över lång tid.

För att beräkna multisjuklighet användes ett index baserat på 45 vanligt förekommande kroniska, icke-smittsamma sjukdomar. Listan inkluderar allt från högt blodtryck, diabetes och cancer till astma, depression och ledbesvär. Varje enskild diagnos hos en individ genererade en poäng. Detta poängssystem gjorde det möjligt att inte bara se om en person var sjuk, utan också att mäta svårighetsgraden av den samlade sjukdomsbyrån.

De studier som genomförts har visat att det finns en stark och dos-graderad association mellan multimorbiditet och VTE. Det innebär att risken för att drabbas av en blodpropp ökar i takt med att antalet kroniska diagnoser stiger. Individer med multimorbiditet uppvisade en mer än tredubblad risk för VTE jämfört med friska individer. För de individer som hade den högsta sjukdomsbördan – definierat som fem eller fler diagnoser – var risken nio gånger högre. Denna riskökning är i paritet med kända, starka riskfaktorer som stora kirurgiska ingrepp eller cancer. Resultaten visar även att multisjuklighet är en oberoende riskfaktor som kvarstår även efter att man tagit hänsyn till faktorer som ålder, kön och utbildningsnivå.

Genom gruppanalys identifierades nio olika sjukdomskluster – grupper av sjukdomar som förekommer tillsammans hos samma individ. Sju av dessa nio kluster visade sig vara kopplade till en ökad risk för VTE. Särskilt framträdande var det kardiometabola klustret (innefattande bland annat högt blodtryck, hjärtsvikt, diabetes och fetma) och det psykiatriska klustret (inkluderande bland annat depression, ångest och missbruk). Att även psykisk ohälsa visar sig vara en stark indikator för propprisk understryker vikten av att betrakta hela patientens situation, snarare än att bara fokusera på traditionella fysiska riskfaktorer.

En annan aspekt som undersökts är om sambandet mellan multisjuklighet och VTE kan förklaras av genetiska faktorer eller delad miljö inom familjer. Genom att studera tvillingar, syskon och kusiner fanns en viss familjär aggregation. Även om de familjära sambanden var relativt svaga, tyder de på att det finns en delad sårbarhet som kan vara både genetisk och miljöbetingad men den individuella och förvärvade sjukdomsbördan väger tyngst.

Eftersom majoriteten av patienter med kroniska sjukdomar handläggs av allmänläkare på vårdcentraler undersöktes det även om det fanns något samband mellan multimorbiditet diagnosticerad i primärvården och risken för VTE. Studien som omfattade över 8 miljoner individer i primärvården bekräftade att den dos-graderade risken finns även i primärvården.

Sammanfattningsvis visar denna avhandling att det finns ett samband mellan multimorbiditet, dess svårighetsgrad och VTE. Multisjuklighet kan därför betraktas som en ny riskfaktor för VTE. Genom att i framtida studier integrera patientens totala sjukdomsbörda och specifika sjukdomskluster i de befintliga bedömningsmodellerna skulle man kunna undersöka om multimorbiditet kan användas i prediktionen av VTE.

List of Papers

Paper I

Ahrén, J., Pirouzifard, M., Holmquist, B., Sundquist, J., Halling, A., Sundquist, K., & Zöller, B. (2023). A hypothesis-generating Swedish extended national cross-sectional family study of multimorbidity severity and venous thromboembolism. *BMJ Open*, 13(6), e072934. <https://doi.org/10.1136/bmjopen-2023-072934>

Paper II

Ahrén, J., Pirouzifard, M., Holmquist, B., Sundquist, J., Sundquist, K., & Zöller, B. (2024). Multimorbidity disease clusters are associated with venous thromboembolism: An extended cross-sectional national study. *Journal of Thrombosis and Thrombolysis*, 57(6), 898–906. <https://doi.org/10.1007/s11239-024-02987-y>

Paper III

Ahrén, J., Pirouzifard, M., Holmquist, B., Sundquist, J., Sundquist, K., & Zöller, B. (2025). Multimorbidity is associated with risk of incident venous thromboembolism – A nationwide proof-of-concept study. *Thrombosis Update*, 18, 100198. <https://doi.org/10.1016/j.tru.2025.100198>

Paper IV

Ahrén, J., Pirouzifard, M., Holmquist, B., Sundquist, J., Sundquist, K., & Zöller, B. (2026). Primary care diagnosed multimorbidity and risk of venous thromboembolism in Sweden. *International Journal of Cardiology: Cardiovascular Risk and Prevention*, 29, 200631. <https://doi.org/10.1016/j.ijcrp.2026.200631>

Author's contribution to the papers

Paper I

J Ahrén participated in the study's conception, design, and statistical analysis. M Pirouzifard, B Holmquist, J Sundquist, A Halling, K Sundquist, and B Zöller all contributed to the interpretation of the data. J Sundquist and K Sundquist were responsible for data acquisition. J Ahrén drafted the manuscript, which was subsequently revised critically by all co-authors. B Zöller and K Sundquist were responsible for funding acquisition. J Ahrén was the corresponding author.

Paper II

J Ahrén contributed to the conception and design. Together with M Pirouzifard, B Holmquist, J Sundquist, K Sundquist, and B Zöller, the results were interpreted. J Sundquist and K Sundquist managed data acquisition. J Ahrén prepared the initial draft of the manuscript, which was subsequently revised critically by all co-authors. B Zöller and K Sundquist were responsible for funding acquisition. J Ahrén was the corresponding author.

Paper III

J Ahrén contributed to conceptualization, methodology, and investigation. M Pirouzifard, B Holmquist, J Sundquist, K Sundquist, and B Zöller all participated in the conceptualization. J Ahrén wrote the original draft, which was subsequently revised critically by all co-authors. B Zöller and K Sundquist were responsible for funding acquisition. J Ahrén was the corresponding author.

Paper IV

J Ahrén participated in the conception and design and performed the data analysis of the primary care data. M Pirouzifard, B Holmquist, J Sundquist, K Sundquist, and B Zöller contributed to the interpretation of data. J Sundquist and K Sundquist were responsible for data acquisition. B Zöller and K Sundquist were responsible for funding acquisition. Jonatan Ahrén prepared the manuscript draft, which was subsequently revised critically by all co-authors. J Ahrén was the corresponding author.

Abbreviations

- APC: Activated protein C
- BMI: Body Mass Index
- CI: Confidence interval
- CIF: Cumulative Incidence Function
- COPD: Chronic obstructive pulmonary disease
- CRP: C-reactive protein
- CTPA: Computed tomographic pulmonary angiography
- DOAC / DOACs: Direct oral anticoagulant(s)
- DVT: Deep vein thrombosis
- F1–F9: Multimorbidity disease clusters
- FVL: Factor V Leiden
- GWAS: Genome-wide association studies
- HR: Hazard ratio
- HRT: Hormone replacement therapy
- IBD: Inflammatory bowel disease
- IBS: Irritable bowel syndrome
- ICD: International Classification of Diseases
- IL-6: Interleukin-6
- IQR: Interquartile range
- IR: Incidence rate
- IRR: Incidence rate ratio
- L1: Landmark 1
- L2: Landmark 2
- LMICs: Low- and middle-income countries
- MR: Mendelian randomization
- NCDs: Noncommunicable disease(s)
- NETs: Neutrophil Extracellular Traps

- NPR: National Patient Register
- OR: Odds ratio
- PCA: Principal component analysis
- PE: Pulmonary embolism
- PIN: Personal identity number
- PTS: Post-thrombotic syndrome
- RCTs: Randomized controlled trials
- SES: Socioeconomic status
- SLE: Systemic lupus erythematosus
- subHR: Subdistribution hazard ratio
- TF: Tissue factor
- TNF- α : Tumor necrosis factor alpha
- TPR: Total Population Register
- VKAs: Vitamin K antagonists
- VTE: Venous thromboembolism
- WHO: World Health Organization

Introduction

Multimorbidity

Concept and Definitions

Management of the increasing prevalence of chronic diseases is a major challenge for governments and healthcare systems worldwide (Barnett et al., 2012). Historically, medical research and education have been organized around a single-disease view, focusing on individual acute and chronic conditions (Barnett et al., 2012; Navickas et al., 2016). This can lead to fragmentation of care and treatment for patients with multiple conditions (Mangin et al., 2012; Navickas et al., 2016). As life expectancy has increased, patients more often present with multiple diseases, multimorbidity (Navickas et al., 2016). This shift has led to a move from single-disease approaches to a multimorbidity-focused approach (Navickas et al., 2016).

The terminology used to describe the coexistence of multiple conditions is often variable and can be confusing (Academy of Medical Sciences, 2018). The term "comorbidity" was first introduced by Feinstein in 1970 (Feinstein, 1970) to describe any distinct additional condition that occurs during the clinical course of a patient who has a specific index disease under study (Academy of Medical Sciences, 2018; Harrison et al., 2021). In contrast, the term "multimorbidity" began to be used more frequently from 1976 onwards to describe the co-occurrence of multiple chronic or acute diseases in a single individual (Harrison et al., 2021; Nicholson et al., 2019). While both terms focus on the occurrence of multiple conditions, "comorbidity" refers to the combined effects of additional conditions in reference to an index chronic condition, such as diabetes or cancer (Harrison et al., 2021; Nicholson et al., 2019; Valderas et al., 2009). In comparison, "multimorbidity" indicates that no single condition takes priority over any of the other co-occurring conditions from the perspective of the patient and the healthcare professional (Harrison et al., 2021; Nicholson et al., 2019). This conceptual distinction is fundamental to the research framework of this thesis, in which multimorbidity is defined and measured as the total burden of disease to assess risk estimates for specific outcomes, such as venous thromboembolism (VTE).

The distinction between these frameworks reflects how different parts of the healthcare system interact with patients (Harrison et al., 2021; Valderas et al., 2009). The concept of comorbidity is traditionally more useful in secondary and tertiary

care settings, where clinical structures are organized around specific body systems or organs (Academy of Medical Sciences, 2018; Harrison et al., 2021). The concept of multimorbidity is more beneficial in primary care, which provides holistic care focused on the patient's overall symptoms, preferences, and priorities (Barnett et al., 2012; Harrison et al., 2021; Valderas et al., 2009). While specialized care might focus on the index disease, a generalist perspective acknowledges that the impact of multimorbidity is a result of the interaction between various diseases and the patient's sociocultural context (Academy of Medical Sciences, 2018; Barnett et al., 2012). To deliver better care, the healthcare system has to be reorganized to move beyond the single-disease view and adopt a multidisease framework for clinical diagnostics and treatment (Ahrén et al., 2023; Navickas et al., 2016).

Despite the need to characterize multimorbidity, there is no single established international consensus on the definition of multimorbidity (Ho et al., 2022; Johnston et al., 2019). Multimorbidity is commonly defined as the coexistence of two or more chronic conditions in the same individual (Johnston et al., 2019; WHO, 2016). This simple cut-off of ≥ 2 conditions has been adopted in epidemiological research to enable comparison across studies and settings (Barnett et al., 2012; Ho et al., 2022; Johnston et al., 2019). The World Health Organization (WHO) similarly defines multimorbidity as the coexistence of two or more long-term conditions (Academy of Medical Sciences, 2018; WHO, 2016). While some researchers have proposed higher cut-offs to identify "complex multimorbidity," consensus remains strongest for the two-disease definition (Ho et al., 2022). In this thesis, this standard definition was applied using a validated score of 45 noncommunicable diseases (NCDs) to capture the total disease burden, though more complex multimorbidity was also studied (Ahrén et al., 2023; Zöller et al., 2023).

Selection and Definition of Chronic Conditions

In this thesis, multimorbidity is defined as the co-occurrence of two or more chronic NCDs. Based on a modified list originally validated by Barnett et al. (2012), 45 clinically important, noninfectious conditions were selected (Zöller et al., 2023). These specific NCDs were chosen because they are common, noninfectious, considerably stable over an individual's life, and contribute significantly to the total disease burden (Zöller et al., 2023). The identification of these conditions relied on the International Classification of Diseases, 10th Revision (ICD-10) codes within Swedish national registers.

The selection and corresponding ICD-10 codes are as follows:

1. Hypertension (I10–I15)
2. Affective disorders (F30–F39)
3. Painful back condition (M50–M54)
4. Asthma (J45–J46)
5. Coronary heart disease (I20–I25)
6. Ulcer disease (K22.1, K25–K28)
7. Diabetes (E10–E14)
8. Thyroid disorders (E00–E07)
9. Connective tissue disease (M05, M06, M08, M09, M30–M36, D86)
10. Hearing loss (H90–H91)
11. Chronic obstructive pulmonary disease (COPD) (J41–J44)
12. Anxiety (F40–F48)
13. Irritable bowel syndrome (IBS) (K58)
14. Cancer (C00–C99)
15. Alcohol misuse disorders (F10)
16. Psychoactive substance misuse (F11–F14, F16, F18, F19)
17. Constipation (K59.0)
18. Cerebrovascular disease (I60–I69)
19. Renal disease (N00–N19, Q61)
20. Diverticular disease of the intestine (K57)
21. Atrial fibrillation (I48)
22. Atherosclerosis (I70–I74, I77)
23. Heart failure (I50, I11.0, I13.0, I13.2)
24. Prostate disease (N40–N42)
25. Glaucoma (H40, H42)
26. Epilepsy (G40, G41)
27. Dementia (F00–F03)
28. Schizophrenia disorders (F20, F21)

29. Psoriasis (L40)
30. Dermatitis or eczema (L20–L30)
31. Inflammatory bowel disease (IBD) (K50, K51)
32. Migraine (G43, G44.0, G44.1)
33. Blindness and poor vision (H53–H54)
34. Chronic sinusitis (J32)
35. Learning disability (F81)
36. Anorexia or bulimia (F50)
37. Bronchiectasis (J47)
38. Parkinson's disease (G20, G21, G22)
39. Multiple sclerosis (G35)
40. Liver disease (K70–K77)
41. Gout (M10)
42. Arthrosis (M15–M19)
43. Osteoporosis (M80–M82)
44. Obesity (E65, E66)
45. Pancreatic disease (K85, K86)

Epidemiology of Multimorbidity

The reported prevalence of multimorbidity varies across epidemiological studies, with estimates ranging from as low as 3.5% to as high as 98.5% (Abebe et al., 2020; Fortin et al., 2012; Schellevis et al., 1993). This substantial variation is largely attributed to methodological differences, particularly the clinical setting (primary care vs. general population), the number and nature of conditions included in the assessment, and the age distribution of the study population (Van den Akker et al., 1998; Fortin et al., 2012). Systematic reviews indicate that studies incorporating a broader list of conditions, typically 12 or more, tend to report higher prevalence estimates than those restricted to only a few diagnoses (Fortin et al., 2012; Ho et al., 2021; Violan et al., 2014). Research conducted in primary care settings reports high prevalence rates; for example, a cross-sectional study in Scotland involving over 1.7 million patients identified an overall prevalence of 23.2% when 40 different conditions were assessed (Barnett et al., 2012). Data from low- and middle-income countries (LMICs) demonstrate an escalating prevalence, with estimates of approximately 36.4%, though results vary markedly across countries, ranging from

0.7% to 81.3%, depending on urbanization and economic development (Asogwa et al., 2022).

The relationship between chronological age and multimorbidity typically follows a pattern, in which prevalence remains low in early adulthood but increases after the age of 40 (Cassell et al., 2018; Van den Akker et al., 1998). Although the percentage of the population affected is highest among the elderly, reaching 83.2% in those aged 85 and older, it is important to note that the absolute number of people living with multimorbidity is often higher in those under 65 years of age due to the demographic structure of the population (Barnett et al., 2012; Cassell et al., 2018). Evidence from younger worker cohorts shows that multimorbidity is already prevalent among young adults, in whom it is associated with significant health-related productivity loss (Troelstra et al., 2020).

Women exhibit a higher prevalence of multimorbidity than men across most age groups (Cassell et al., 2018). Primary care data indicate that the prevalence in females is approximately 30.0% compared to 24.4% in males (Cassell et al., 2018). While women's higher life expectancy contributes to this trend, they also exhibit different patterns of disease composition (Schäfer et al., 2010; Violan et al., 2014). Schäfer et al. used factor analysis to demonstrate that these compositions are gender-specific; women are more frequently represented in patterns involving mental health, musculoskeletal disorders (such as arthrosis), and chronic pain syndromes, whereas men more commonly present with cardiometabolic conditions (Schäfer et al., 2010).

Socioeconomic status (SES) is a predictor of multimorbidity in high-income countries (Marmot, 2005). Individuals with lower levels of educational attainment and lower income not only have a higher overall risk of developing multimorbidity but also tend to develop it 10 to 15 years earlier than those in wealthier groups (Barnett et al., 2012). This difference is often explained by the “inverse care law”, which was originally characterized by Hart (1971), that medical care is most accessible to those who need it least, and by the higher prevalence of lifestyle risk factors in lower SES groups (Hart, 1971; Marmot, 2005; Mercer et al., 2012). In some LMIC settings, however, the trend can be reversed, with higher income being associated with increased multimorbidity due to rapid transitions in diet and the adoption of inactive lifestyles (Álvarez-Gálvez et al., 2023; Asogwa et al., 2022).

The geographical location of residence influences the risk of multimorbidity (Barnett et al., 2012; Makovski et al., 2019). Multimorbidity is generally more prevalent in urban areas, which can be linked to environmental exposures such as air pollution, increased population density, and reduced opportunities for physical activity (Violan et al., 2014). Neighborhood-level deprivation has a major effect on health outcomes; residents of socioeconomically disadvantaged areas carry a heavier disease burden regardless of whether they live in rural or urban settings (Barnett et al., 2012). In regions like Scotland, the association of physical and

mental health multimorbidity was found to be stronger in deprived areas compared to wealthy ones, highlighting the impact of social factors (Barnett et al., 2012).

Healthcare Utilization and Clinical Management

In most healthcare systems, primary care serves as the main center for managing chronic diseases, and multimorbid patients account for the majority of consultations in this setting (Barnett et al., 2012; Salisbury et al., 2011; Starfield et al., 2003; Van den Akker et al., 1998). The frequency of primary care visits is highly related to the degree of multimorbidity (Schellevis et al., 1994; Starfield et al., 2003). Continuity of care is considered a major factor in managing these patients, as a long, personal patient-doctor relationship creates trust between patients and doctors (Luijckx et al., 2012; Wallace et al., 2015). Strong relational continuity has been associated with improved preventive care and a reduction in preventable hospital admissions (Nyweide et al., 2013; Wallace et al., 2015).

The impact of multimorbidity in emergency care settings is important as these patients often present with more severe illnesses and higher acute needs (Blayney et al., 2024; McParland et al., 2022). Individuals with multimorbidity are more likely to arrive by ambulance and are frequently triaged into more urgent categories compared to those without multimorbidity (Blayney et al., 2024). These patients tend to spend a longer duration of time in the emergency department due to their more complex needs (Blayney et al., 2024). Poor continuity in primary care can lead to avoidable emergency visits, as fragmented systems may fail to identify early signs of worsening in patients with multimorbidity (Blayney et al., 2024; Nyweide et al., 2013; Wallace et al., 2015).

There is an association between the severity of multimorbidity and the risk of unplanned hospital admissions (Condelius et al., 2008; Payne et al., 2013; Rodrigues et al., 2022). Data suggest that these individuals account for a disproportionately large proportion of both unplanned and potentially preventable hospitalizations (Payne et al., 2013). Multimorbid patients often face longer hospital stays (Librero et al., 1999; Rodrigues et al., 2022), which increase the risk of functional loss, stress, and cognitive impairment (Rodrigues et al., 2022). The risk of hospital readmission is significantly higher in older adults with multimorbidity (Librero et al., 1999; Rodrigues et al., 2022).

Fragmentation of care often results from multiple specialists focusing on single organs rather than the whole person (Luijckx et al., 2012; Salisbury et al., 2018). Effective management requires multidisciplinary care that involves various professionals and a team around the patient (Palmer et al., 2018). International consensus highlights that a primary care system providing complete and integrated care is necessary to avoid the fragmentation that characterizes the experience of many multimorbid patients (Rodrigues et al., 2022; Salisbury et al., 2018).

Most current clinical practice guidelines are based on evidence derived from randomized controlled trials that routinely exclude older patients and those with multimorbidity (Fortin et al., 2006; Tinetti et al., 2004; Wallace et al., 2015). These guidelines maintain a disease-specific focus that optimizes outcomes for a single condition but may be inappropriate when applied to a patient with multimorbidity (NICE, 2016; Tinetti et al., 2004). This single-disease approach fails to account for the interactions between different diseases and the medications used to treat them (NICE, 2016).

Patients with multimorbidity face the risk of receiving conflicting recommendations, where following a guideline for one disease may aggravate another (Dumbreck et al., 2015; Tinetti et al., 2004; Wallace et al., 2015). This may result in polypharmacy, which increases the risk of adverse drug events, drug-drug interactions, and poor treatment adherence (Gandhi et al., 2003; Tinetti et al., 2004; Wallace et al., 2015). The cumulative treatment burden can be overwhelming for patients (Wallace et al., 2015).

International organizations have begun to shift from single-disease frameworks toward multimorbidity-focused approaches (Palmer et al., 2018; World Health Organization [WHO], 2016). For example, the NICE guidelines in the UK emphasize shared decision-making and the development of individualized management plans based on patient priorities and goals (NICE, 2016). There are also new strategies, such as the 3D model (Dimensions of Health, Depression, and Drugs), which focus on improving quality of life and functional optimization rather than meeting disease-specific targets (Salisbury et al., 2018).

These international perspectives argue that management should prioritize the patient's overall health and well-being, acknowledging that for some complex patients, less intensive treatment may represent better clinical judgment (NICE, 2016; Wallace et al., 2015).

Risk Factors for Multimorbidity

The most well-established driver of multimorbidity is increasing age (Barnett et al., 2012; Fortin et al., 2012; Violan et al., 2014). Studies consistently demonstrate a significant positive association between older age and the number of accumulated chronic conditions, with prevalence rates reaching high levels in individuals aged 65 years and older (Barnett et al., 2012; Violan et al., 2014). The age of onset is significantly influenced by socioeconomic factors; individuals living in the most deprived areas often develop multimorbidity 10–15 years earlier than their most affluent peers (Barnett et al., 2012; Kingston et al., 2018).

The influence of sex on multimorbidity prevalence has been reported in different settings and study populations (Fortin et al., 2012; Violan et al., 2014). Substantial

evidence indicates that women generally have higher levels of multimorbidity than men (Barnett et al., 2012; Cassell et al., 2018).

Tobacco use is a risk factor that contributes to the development of multimorbidity through its causal links with cardiovascular diseases, respiratory diseases, and cancer (The Academy of Medical Sciences, 2018; Tazzeo et al., 2023). While some studies show inconsistent results, potentially due to survival bias or failure to adjust for confounders, the overall trend indicates that both current and former smokers have increased odds of accumulating multiple chronic conditions compared to nonsmokers (The Academy of Medical Sciences, 2018; Tazzeo et al., 2023).

Obesity, which is often measured by body mass index (BMI), is associated with an increased risk of incident multimorbidity (Baltramonaityte et al., 2023; Tazzeo et al., 2023; Wikström et al., 2015). Mendelian randomization (MR) studies have established a causal link between increased BMI and "psycho-cardiometabolic" clusters, including coronary artery disease, type 2 diabetes, and depression (Baltramonaityte et al., 2023). The risk follows a dose-response relationship, with severely obese individuals experiencing substantially higher hazards of cardiometabolic multimorbidity development compared to those with a normal weight (Kivimäki et al., 2017; Tazzeo et al., 2023). Both high baseline BMI and short-term weight gain are associated with accelerated disease accumulation (Tazzeo et al., 2023).

Physically inactive behavior is a determinant of multiple chronic conditions, including cardiometabolic and musculoskeletal disorders (Tazzeo et al., 2023; Wikström et al., 2015). Research indicates an inverse dose-response relationship between physical activity levels and multimorbidity, with higher activity reducing the odds of developing new conditions (The Academy of Medical Sciences, 2018; Tazzeo et al., 2023). A longitudinal study from England demonstrates that individuals engaging in physical activity have lower odds of incident multimorbidity compared to those who are physically inactive (Dhalwani et al., 2017). The relationship is often bidirectional, as the presence of multiple conditions - particularly those involving pain or mobility issues - can reduce an individual's capacity for exercise, thereby creating a cycle that further worsens health decline (Tazzeo et al., 2023).

Mental health conditions, particularly depression and anxiety, frequently cluster with chronic physical diseases (Barnett et al., 2012; Smith et al., 2014). This relationship is recognized as bidirectional; while the burden of multiple physical illnesses often leads to psychological distress, pre-existing mental disorders are strong predictors of future physical multimorbidity (Barnett et al., 2012; The Academy of Medical Sciences, 2018; Tazzeo et al., 2023). For example, depressive symptoms in early adulthood are significantly associated with the later development of physical conditions such as diabetes and cardiovascular disease (Arias-de la Torre et al., 2021). The mechanisms underlying this link may include shared biological

pathways, such as chronic low-grade inflammation and immune system dysfunction (Khandaker et al., 2020; Zazzara et al., 2025), as well as behavioral factors like reduced treatment compliance (Asogwa et al., 2022; Baltramonaityte et al., 2023).

Socioeconomic deprivation is also a driver of multimorbidity, contributing to health inequalities (Barnett et al., 2012; Violan et al., 2014). Lower SES, education, and income are consistently associated with higher rates of multimorbidity (Álvarez-Gálvez et al., 2023; Barnett et al., 2012; Tazzeo et al., 2023). Additionally, social isolation and a lack of social support are associated with increased loneliness and a higher risk of multimorbidity onset (Hajek et al., 2020).

Family history is also a risk factor for multimorbidity, resulting from both shared genetic susceptibility and environmental exposures (Zöller et al., 2023). Data demonstrate that multimorbidity aggregates within families, showing a graded relationship with genetic resemblance, where risks are highest among twins and full siblings (Zöller et al., 2023). Household factors may have an influence, but the associations among distant relatives who typically do not share a household further support a hereditary component (Zöller et al., 2023).

Multimorbidity Patterns and Disease Clusters

The identification of nonrandom disease clusters is important for investigating shared mechanisms of disease and to develop more effective treatment strategies (Ferris et al., 2025; Whitty & Watt, 2020). These patterns suggest underlying pathological processes, such as shared genetic factors, chronic systemic inflammation, or environmental triggers, which drive the co-occurrence of specific conditions (Zöller et al., 2023). By recognizing stable clusters, clinicians can use this information to move toward a more person-centered model of care (Busija et al., 2019; Rajoo et al., 2021; Schäfer et al., 2010). Furthermore, understanding the associations between diseases that occur more frequently than expected by chance can help identify pathways for secondary prevention and earlier screening for these conditions (Prados-Torres et al., 2014; Van den Akker et al., 1998).

The identification of multimorbidity patterns relies on unsupervised, data-driven statistical techniques that aim to partition large datasets based on disease co-occurrence (Ferris et al., 2025; Ng et al., 2018; Van den Akker et al., 1998).

There are several analytical approaches, including hierarchical cluster analysis, latent class analysis, and factor analysis (Ferris et al., 2025; Ng et al., 2018; Schäfer et al., 2010). Hierarchical cluster analysis groups conditions based on proximity measures, while latent class analysis is a person-centered approach that classifies individuals into homogeneous subgroups (Ferris et al., 2025; Møller et al., 2020). Exploratory factor analysis and principal component analysis (PCA) are factor-based approaches that identify latent structures in disease data (Busija et al., 2019; Zöller et al., 2023) and use eigenfunctions to interpret patterns in dichotomous

matrices (Tinkler, 1972). In this thesis, an initial PCA followed by factor analysis, with a principal factor method and an oblique rotation, was used to identify disease clusters at the individual level (Ahrén et al., 2024; Zöller et al., 2023).

Systematic reviews have demonstrated that certain multimorbidity patterns emerge consistently across different populations, suggesting universal disease pathways (Busija et al., 2019; Ferris et al., 2025).

The most reproducible and prevalent pattern in the existing scientific literature is the cardiometabolic cluster (Ferris et al., 2025; Rajoo et al., 2021; Schäfer et al., 2010). This pattern is typically characterized by the co-occurrence of hypertension, diabetes mellitus, dyslipidemia, and obesity (Busija et al., 2019; Prados-Torres et al., 2012). It reflects the well-established pathophysiological links of the metabolic syndrome, involving shared risk factors such as insulin resistance and chronic inflammation (Reaven 1988; Eckel et al., 2005).

A second highly replicable pattern is the neuropsychiatric or mental health cluster (Busija et al., 2019; Ferris et al., 2025). This group commonly includes mood and anxiety disorders, such as depression and anxiety, and often extends to neurological conditions like dementia or Parkinson's disease (Busija et al., 2019; Rajoo et al., 2021). Research suggests that these conditions often group along an identifiable continuum, supporting the hypothesis of shared neurobiological pathways (Busija et al., 2019; Ferris et al., 2025; Kessler et al., 2005).

The musculoskeletal pattern is frequently reported and primarily consists of osteoarthritis, joint diseases, and painful back conditions (Busija et al., 2019; Prados-Torres et al., 2014). This pattern is often associated with advanced age and obesity, though it frequently clusters with mental health conditions due to the impact of chronic pain on psychological distress (Álvarez-Gálvez et al., 2023; Prados-Torres et al., 2014).

Additional patterns identified in the literature include respiratory diseases, allergic diseases, and gastrointestinal cancer patterns (Ferris et al., 2025; Ng et al., 2018; Rajoo et al., 2021). For example, atopic patterns are characterized by seasonal allergies and dermatitis (Álvarez-Gálvez et al., 2023; Ng et al., 2018). Degenerative patterns that feature sensory impairments such as vision and hearing loss are frequently observed in elderly populations (Busija et al., 2019; Rajoo et al., 2021). These clusters highlight that multimorbidity is not a random accumulation of diseases, but a structured phenomenon driven by shared environmental or genetic triggers (Álvarez-Gálvez et al., 2023; Møller et al., 2020).

In the present thesis, nine multimorbidity disease clusters were identified, F1–F9 (Ahrén et al., 2024; Zöller et al., 2023). The identified clusters were: F1 (cardiometabolic diseases), hypertension, heart failure, coronary heart disease, diabetes, obesity, atrial fibrillation, gout, atherosclerosis, and renal disease; F2 (psychiatric diseases), affective disorders, anxiety, schizophrenia disorders,

psychoactive substance misuse, alcohol misuse disorders, anorexia or bulimia; F3 (digestive system diseases), IBD, liver disease, pancreatic disease, and ulcers; F4 (neurological/cancer), epilepsy, cancer, cerebrovascular disease, blindness and poor vision, and impaired hearing or hearing loss; F5 (connective tissue/autoimmune), connective tissue disease, osteoporosis, thyroid disorders, and psoriasis; F6 (prostate/musculoskeletal), prostate disease, arthrosis, diverticular disease of the intestine, chronic sinusitis, and back pain; F7 (neurodegenerative/bowel), bronchiectasis, learning disability, Parkinson's disease, glaucoma, and IBS; F8 (respiratory/atopic), asthma, COPD, dermatitis and eczema, constipation, and migraine; and F9 (neurodegenerative) dementia and multiple sclerosis (Ahrén et al., 2024; Zöller et al., 2023).

The identified clusters were used because they represent clinically observed and previously described clusters. The validity of these patterns is supported by the fact that they have been previously seen in multimorbidity research, indicating that they represent pathways of disease progression rather than random co-occurrences (Busija et al., 2019; Prados-Torres et al., 2014).

F1 (Cardiometabolic diseases): This pattern is a reproducible cluster in the literature and aligns with the metabolic syndrome (Busija et al., 2019; Prados-Torres et al., 2014). It is based on shared etiological mechanisms such as insulin resistance, vascular damage, and chronic systemic inflammation (Reaven, 1988; Eckel et al., 2005; Schäfer et al., 2010), and its clinical impact is characterized by an important association with increased all-cause mortality and a significant reduction in life expectancy (Di Angelantonio et al., 2015).

F2 (Psychiatric diseases): The grouping of affective disorders, anxiety, and schizophrenia aligns with previous findings (Kessler et al., 2005) and has been shown in previous studies (Schäfer et al., 2010). These results suggest that these conditions may be different manifestations of the same underlying neurobiological distress (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Castro-de-Araujo et al., 2022; Busija et al., 2019).

F3 (Digestive system diseases): The co-occurrence of IBD and liver disease reflects recognized immunological and physiological links between the gut and the hepatobiliary system (Karlsen et al., 2017; Tilg & Moschen, 2010). Similar digestive patterns have been consistently identified as significant nonrandom associations in previous studies (Prados-Torres et al., 2012, 2014).

F4 (Neurological/Cancer): This cluster shows the co-occurrence of epilepsy, stroke, and malignancy. This relationship is supported by evidence of genetic similarity and shared biological pathways between certain cancers and neurological conditions (Melamed et al., 2015; Navi et al., 2017). Sensory impairments, such as hearing loss, have been reported to correlate specifically with cerebrovascular risk (Khosravipour et al., 2021).

F5 (Connective tissue/Autoimmune): The association among thyroid disorders, psoriasis, and connective tissue diseases is often driven by systemic autoimmune dysregulation (Ayala-Fontánez et al., 2016; Mackay, 2009). The inclusion of osteoporosis in this cluster may reflect iatrogenic factors, such as the long-term use of corticosteroids, which is common in the treatment of autoimmune conditions (Smith, 1990; Van Staa et al., 2000).

F6 (Prostate/Musculoskeletal): This pattern groups arthrosis and back pain with prostate disease patterns identified in other aging populations (Prados-Torres et al., 2012, 2014).

F7 (Neurodegenerative/Bowel): The link between Parkinson's disease and IBS has previously been investigated (Zhang et al., 2021). It supports the "gut-brain axis" hypothesis, which suggests that neurodegenerative processes may manifest through gastrointestinal dysfunction significantly earlier than motor symptoms appear (Braak et al., 2003).

F8 (Respiratory/Atopic): This "atopic" pattern, combining asthma, COPD, and dermatitis, may reflect a shared systemic inflammatory state and genetic predisposition (Álvarez-Gálvez et al., 2023; Barnes, 2008; Spergel & Paller, 2003). Additionally, the inclusion of migraine in this group is supported by established comorbid relationships between migraine and asthma (Aamodt et al., 2007).

F9 (Neurodegenerative): This cluster focuses on chronic neuroinflammatory and neurodegenerative processes that result in cognitive and functional decline, which have previously been described (Chiaravalloti & DeLuca, 2008).

The familial aggregation observed in seven of these clusters (F1–F6, F8) also reinforces their legitimacy as structured disease clusters with a significant genetic component (Zöller et al., 2023).

Etiology and Biological Mechanisms

The etiology of multimorbidity is complex and multifactorial, involving a complex interaction between acquired risk factors, such as aging and lifestyle, and inherited genetic susceptibility (Barnett et al., 2012; North et al., 2023; Zöller et al., 2023). Understanding the biological mechanisms driving the simultaneous development of diverse health conditions is critical for improving risk prediction and personalizing preventive strategies (Zazzara et al., 2025).

The clustering of NCDs is nonrandom, suggesting that shared pathogenetic mechanisms often link conditions that appear to have different pathophysiologies (Barnes, 2015; Dong et al., 2021). A mechanism in the development of multimorbidity is chronic inflammation, often referred to as "inflammaging" in the context of biological aging (Franceschi et al., 2018; St. Sauver et al., 2022). Chronic low-grade systemic inflammation is characterized by elevated proinflammatory

cytokines and has been associated with an increased number of chronic conditions (Fabbri et al., 2015; Friedman et al., 2019; St. Sauver et al., 2022). This inflammatory state acts as a common driver of various disease clusters, including cardiometabolic, respiratory, and musculoskeletal disorders (Barnes, 2015; Li et al., 2025). For example, inflammatory processes in adipose tissue can trigger endothelial dysfunction and remodeling, leading to circulatory and metabolic burden that contributes to multiple cardiometabolic diseases (Li et al., 2025; Saltiel & Olefsky, 2017).

Metabolic dysregulation represents another shared pathway, particularly for the cardiometabolic cluster, which includes hypertension, type 2 diabetes, and coronary artery disease (Eckel et al., 2005; Li et al., 2025; Reaven, 1988). Obesity is a modifiable predictor that drives metabolic impairment through mechanisms such as insulin resistance and lipotoxicity (Li et al., 2025; North et al., 2023; Song et al., 2024; Ye, 2013). MR studies have established a causal association between modifiable factors, specifically BMI, smoking, and glycemic control, and the development of cardiometabolic and cardiopulmonary multimorbidity (Li et al., 2025; North et al., 2023; Song et al., 2024). These metabolic disruptions often work together with chronic inflammation to accelerate physiological aging and the accumulation of biological deficits (Fabbri et al., 2015; Langenberg et al., 2023).

The identification of biological markers is important for early diagnosis and monitoring the multimorbidity burden (Wessman et al., 2022; Zazzara et al., 2025). Inflammatory biomarkers have been studied, with interleukin-6 (IL-6) emerging as an important indicator (Fabbri et al., 2015; St. Sauver et al., 2022; Zazzara et al., 2025). Higher baseline levels of IL-6, as well as a steeper increase in IL-6 over time, are significantly associated with an accelerated rate of acquiring additional chronic diseases (Fabbri et al., 2015). Other relevant inflammatory markers include C-reactive protein (CRP), which has been associated with the number of health conditions, and fibrinogen, which is biologically linked to the IL-6-driven acute-phase response (Oliviera et al., 2025; Friedman et al., 2019). Adiponectin, a cytokine secreted by adipocytes with anti-inflammatory and insulin-sensitizing effects, is significantly reduced in women with multimorbidity (Oliviera et al., 2025).

Metabolic markers also provide insight into multimorbidity risk and severity (Li et al., 2025). Glycated hemoglobin and fasting blood glucose are linked to multimorbidity, which shows the importance of glycemic control (Stepanova et al., 2015; Zazzara et al., 2025). MR studies have established causal links between higher fasting insulin levels and the development of psycho-cardiometabolic multimorbidity (Baltramonaityte et al., 2023). Lipid metabolism indicators, such as triglycerides and low-density lipoprotein cholesterol, are associated with the onset of cardiovascular and metabolic clusters (Li et al., 2025; Zazzara et al., 2025). Markers of kidney and liver function, such as cystatin C and serum alanine

aminotransferase, have been shown to predict multimorbidity and related mortality (Zazzara et al., 2025).

A hereditary component of multimorbidity has been established, demonstrating that it aggregates in families based on the degree of relatedness (Zöller et al., 2023). Approximately 46% of multimorbidity among common diseases is estimated to be genetically interpretable through shared genomic loci or overall genetic architectures (Dong et al., 2021). The phenomenon of pleiotropy, where single genetic variants or loci are associated with multiple diseases, provides an explanation for the clustering of conditions in multimorbidity (Langenberg et al., 2023; Murrin et al., 2025; Zöller et al., 2023). Genome-wide association studies (GWAS) have identified numerous pleiotropic loci, such as the human leukocyte antigen region on chromosome 6, which is relevant for various autoimmune and inflammatory diseases (Dong et al., 2021). An example is the *IL6R* gene, where variants are associated not only with rheumatoid arthritis but also with IBD, atrial fibrillation, and coronary heart disease (Langenberg et al., 2023). Specific candidate genes related to lipid metabolism, immune function, and the stress response have been implicated in the cardiometabolic and psychiatric clusters (Baltramonaityte et al., 2023; Li et al., 2025; Zhao et al., 2024). These genetic correlations suggest that many diseases share common molecular pathways, and mapping these clusters may provide valuable insights into drug discovery and the identification of high-risk families for preventive interventions (Dong et al., 2021; Murrin et al., 2025; Zöller et al., 2023).

Venous Thromboembolism

Definition and Classification

Deep vein thrombosis (DVT) is defined as the formation of a blood clot in the deep venous system, most frequently occurring in the lower extremities, such as the leg or pelvis (Heit, 2015; Khan et al., 2021). The scientific foundation of this disease entity dates back to Rudolf Virchow, who was the first to define the condition as “Embolia” and explain that pulmonary emboli originate from venous thrombi (Dalen, 2002; Virchow, 1856). While many cases remain asymptomatic, symptomatic DVT often presents with leg pain, swelling, and localized tenderness (Khan et al., 2021; Turetz et al., 2018).

Pulmonary embolism (PE) constitutes the most severe and potentially lethal manifestation (Riva et al., 2015; Turetz et al., 2018). It occurs when a thrombus detaches from its point of origin - most commonly a DVT in the lower extremities - and travels through the venous circulation to the pulmonary arterial system (Khan et al., 2021; Turetz et al., 2018). The clinical presentation of PE varies widely, ranging from incidentally discovered asymptomatic cases to massive PE

characterized by acute right ventricular failure, hemodynamic collapse, and sudden death (Khan et al., 2021; Turetz et al., 2018).

The classification of VTE also encompasses other venous thrombotic events occurring in less common sites (Heit et al., 2016; Khan et al., 2021). These include thrombosis of the upper extremities, as well as of the cerebral, splanchnic, mesenteric, renal, and hepatic veins (Heit et al., 2016; Khan et al., 2021). Although historically considered a localized condition, superficial vein thrombosis is now recognized as an independent risk factor for the development of subsequent DVT or PE (Heit, 2015; Heit et al., 2016).

Pathophysiology

The model for understanding VTE pathogenesis remains Virchow's triad (Virchow, 1856), which identifies venous stasis, vessel wall injury, and hypercoagulability as the primary drivers of thrombosis (Dalen, 2002; Kumar et al., 2010). Molecular biology suggests that these components are not isolated but interactive systems that regulate hemostatic potential (Wolberg et al., 2012). VTE can be seen as a multifactorial disease where multiple events must happen to exceed an individual's personal thrombosis threshold (Esmon, 2009; Heit, 2015; Rosendaal, 1999). This implies that a single clinical risk factor is often insufficient to trigger a thrombotic event (Esmon, 2009). VTE risk assessment must account for the additive and often synergistic interactions between these factors (Wolberg et al., 2012).

Venous stasis is a primary contributor to VTE, particularly in hospitalized and immobile populations (Heit, 2015; Kumar et al., 2010). Thrombosis is initiated primarily within the valve sinuses of deep veins, areas characterized by disturbed blood flow and low shear rates (Esmon, 2009; Wolberg et al., 2012). An autopsy study showed that the venous valvular sinus is the primary site for the initiation of thrombus formation (Sevitt, 1974). Local stasis induces regional hypoxia and hemoconcentration, triggering endothelial cell activation (Colling et al., 2021; Esmon, 2009). This hypoxic microenvironment upregulates adhesion molecules like P-selectin while downregulating natural anticoagulants, such as thrombomodulin (Esmon, 2009; Wolberg et al., 2012). Stasis increases the time in the vessel of activated coagulation factors, preventing their interaction with anticoagulants (Esmon, 2009). Venographic evidence has demonstrated that contrast media can remain in the valve sinuses for an average of 27 minutes post-injection, providing a mechanical basis for the local accumulation of procoagulant factors (McLachlin et al., 1960). Clinical manifestations include immobilization from surgery, limb paralysis, and prolonged travel (Heit, 2015; Turetz et al., 2018). Data by Kakkar et al. (1969) provided systematic evidence of the high natural incidence of these postoperative thrombi in the absence of prophylaxis.

In VTE, endothelial activation or dysfunction plays a more prominent role than mechanical injury of the vessel wall (Colling et al., 2021; Wolberg et al., 2012). While direct injury occurs during major trauma, small injuries result from systemic inflammation or metabolic changes, causing the shedding of the endothelial glycocalyx, a protective carbohydrate-rich layer on the endothelial surface (Colling et al., 2021; Kumar et al., 2010). The loss of this glycocalyx reduces antithrombin III binding sites and impairs the activated protein C (APC) pathway (Colling et al., 2021; Esmon, 2009). This change from an inactive, antithrombotic surface to an active, prothrombotic one is a step toward developing VTE (Colling et al., 2021). Activated endothelial cells also enable the recruitment of leukocytes and platelets, and increase procoagulant activity (Wolberg et al., 2012).

Hypercoagulability, or thrombophilia, refers to alterations in blood composition predisposing to thrombus formation (Dalen, 2002; Wolberg et al., 2012). These states are either inherited, such as protein C and protein S deficiencies (Comp & Esmon, 1984; Griffin et al., 1981), Factor V Leiden (FVL) (Bertina et al., 1994; Dahlbäck et al., 1993), and prothrombin G20210A (Poort et al., 1996), or acquired through conditions such as cancer (Heit, 2015; Turetz et al., 2018). Tumors contribute to hypercoagulability by producing procoagulant substances and shedding tissue factor (TF), a primary cellular trigger of the coagulation cascade, on circulating microparticles (Colling et al., 2021; Turetz et al., 2018). Hormonal states, including pregnancy and oral contraceptive use, promote hypercoagulability by increasing the hepatic production of procoagulant factors, reducing levels of natural anticoagulants such as protein S, and impairing fibrinolysis (Colling et al., 2021; Turetz et al., 2018). The synergistic effect is high; for instance, the risk of VTE increases 35-fold in FVL carriers using oral contraceptives (Esmon, 2009; Vandenbroucke et al., 1994).

Inflammation is recognized as a central driver of VTE, acting as a common pathway through which risk factors such as obesity and infection trigger thrombosis (Branchford & Carpenter, 2018; Saghazadeh & Rezaei, 2016). This shift toward immunothrombosis characterizes VTE as an intravascular effector of innate immunity (Engelmann & Massberg, 2013). Chronic inflammatory conditions, such as IBD and systemic lupus erythematosus (SLE), are associated with a substantially increased VTE risk (Branchford & Carpenter, 2018; Saghazadeh & Rezaei, 2016). High levels of biomarkers such as CRP, Tumor necrosis factor alpha (TNF- α), and IL-6 have been linked to VTE (Branchford & Carpenter, 2018; Lutsey & Zakai, 2022). These cytokines promote a prothrombotic state by inducing TF expression on monocytes and endothelial cells (Branchford & Carpenter, 2018). Chronic inflammation also triggers the release of neutrophil extracellular traps (NETs), a host defense mechanism described by Brinkmann et al. (2004). These web-like structures provide a physical scaffold for platelet aggregation and fibrin deposition and have been established as a critical component for the initiation and stability of venous thrombi (Colling et al., 2021; Fuchs et al., 2010; Saghazadeh & Rezaei, 2016).

Diagnosis

The clinical signs and symptoms of VTE are often nonspecific (Khan et al., 2021). Typical symptoms of DVT include unilateral leg pain (occurring in 80%–90% of cases), swelling (80%), and localized tenderness on palpation (Khan et al., 2021; Sandler et al., 1984). For PE, typical symptoms are rapid-onset dyspnea (80%) or pleuritic chest pain (60%–70%), although tachycardia and cough are also frequently seen (Khan et al., 2021; Stein et al. 1991).

Atypical symptoms and subclinical presentations are common, potentially leading to underdiagnosis (Stein et al., 2007). Symptoms may be mild or even absent in patients where the embolism is limited to the segmental pulmonary branches (Stein et al., 2007). Only approximately half of patients with PE exhibit objectively confirmed DVT at the time of PE diagnosis (Khan et al., 2021; van Langevelde et al., 2013).

Since there is a poor correlation between clinical signs and the objective presence of a thrombus, the use of clinical prediction models is important (Sandler et al., 1984). Pre-test probability guides the selection of further diagnostic investigations (Huisman & Klok, 2013; Wells et al., 1997). The Wells score is the most widely used clinical guide, categorizing patients into "likely" or "unlikely" groups for both DVT and PE (Wells et al., 1997; Wells et al., 2000; Wells et al., 2003). Other validated tools include the revised Geneva score and the YEARS criteria, which integrate clinical variables with biomarkers (Huisman & Klok, 2013; Khan et al., 2021; van der Hulle et al., 2017). For hospitalized medical patients, the Padua Prediction Score and the Improve score provide a point-based system to identify those at high risk of VTE complications (Barbar et al., 2010; Spyropoulos et al., 2011).

Objective imaging is required to confirm a VTE diagnosis once clinical suspicion is established (Khan et al., 2021). Ultrasonography is the first-line and standard imaging modality for DVT (Khan et al., 2021). The primary diagnostic criterion is the failure to compress the vein lumen with the ultrasound probe, which confirms the presence of a thrombus (Sandler et al., 1984; Khan et al., 2021). For the diagnosis of PE, computed tomographic pulmonary angiography (CTPA) is the first-line of diagnostics (Huisman & Klok, 2013; Stein et al., 2006). CTPA offers high sensitivity and specificity, particularly for segmental and centrally located emboli (Huisman & Klok, 2013; Stein et al., 2006). Ventilation-perfusion scintigraphy remains an alternative for patients with contraindications to contrast dye or other contraindications (Huisman & Klok, 2013; Khan et al., 2021).

Diagnostic management relies on integrated algorithms that combine clinical probability assessment, D-dimer testing, and imaging (Huisman & Klok, 2013; van Belle et al., 2006). In patients categorized as "unlikely" to have VTE, a negative D-dimer test can safely rule out the diagnosis without the need for radiological evaluation (Khan et al., 2021; Wells et al., 2003). To improve efficiency and reduce

overdiagnosis, age-dependent D-dimer cut-offs (age $\times$ 10 $\mu\text{g/L}$) have been implemented for patients older than 50 years (Huisman & Klok, 2013; Khan et al., 2021; Righini et al., 2014). Imaging is reserved for those with a “likely” clinical probability or elevated D-dimer concentrations (Huisman & Klok, 2013; Kearon et al., 2019). This sequential approach has been shown to reduce unnecessary CTPA examinations by 20%–30% while maintaining diagnostic safety (Huisman & Klok, 2013; Righini et al., 2014; van Belle et al., 2006).

Epidemiology

The annual incidence of acute VTE in Western populations is estimated to be between 1–2 cases per 1,000 individuals (Khan et al., 2021; Lutsey & Zakai, 2022). In the United States, the incidence of diagnosed VTE is approximately 1.17 per 1,000 person-years, though the true incidence is likely higher due to cases remaining undiagnosed or being identified only at autopsy (Anderson et al., 1991; Heit, 2015; Turetz et al., 2018). In Norway, the incidence rate for a first VTE event has been reported at approximately 1.43 per 1,000 person-years (Naess et al., 2007), whereas a large Swedish nationwide registry study reported an overall annual incidence of 1.05 per 1000 inhabitants (Glise Sandblad et al., 2022). Lifetime risk estimates suggest that approximately 1 in 12 individuals in Western regions will be diagnosed with VTE during their lifetime (Lutsey & Zakai, 2022). Approximately two-thirds of symptomatic VTE cases manifest as DVT alone, while the remaining one-third present as PE (Anderson et al., 1991; White, 2003).

The incidence of VTE is strongly age-dependent and rises exponentially with increasing age (Heit, 2015; Naess et al., 2007). VTE is rare during childhood, with an incidence of approximately 1 per 100,000, but increases to nearly 1% per year among individuals older than 70 years of age (Khan et al., 2021; Rosendaal, 1999). The overall age-adjusted incidence rate is generally higher in men than in women, with a reported sex ratio of approximately 1.2:1 (Anderson et al., 1991; Heit, 2015). Sex differences vary throughout life, and women exhibit a higher risk during their reproductive years (ages 20–40) due to exposures such as oral contraceptives (Lidegaard et al., 2011) and pregnancy (Khan et al., 2021; Lutsey & Zakai, 2022). Men have a higher incidence in older age groups, which may be partially explained by differences in basal risk factors such as height (Lutsey & Zakai, 2022; Zöller et al., 2017a).

VTE is associated with high rates of short-term mortality and long-term disability (Anderson et al., 1991; Khan et al., 2021). Approximately 20% of patients with PE die within one year of diagnosis, often due to underlying comorbidities such as malignancy (Khan et al., 2021; Sogaard et al., 2014; Tagalakakis et al., 2013). VTE is a chronic illness characterized by frequent recurrence; approximately 30% of patients develop a recurrent event within 10 years following the initial episode (Heit, 2015; White, 2003). Long-term complications are common among survivors, with

post-thrombotic syndrome (PTS) affecting between 20%–50% of patients after proximal DVT (Brandjes et al., 1997; Galanaud et al., 2018; Kahn et al., 2008). Severe PTS, which can include venous claudication or leg ulcers, occurs in 5%–10% of cases and significantly impairs quality of life (Galanaud et al., 2018). Additionally, chronic thromboembolic pulmonary hypertension affects up to 3% of survivors of acute PE (Khan et al., 2021; Pengo et al., 2004).

Risk Factors

VTE is characterized as a complex, multifactorial disease. The pathogenesis arises from the interaction between a polygenic background and environmental risk factors (Lander & Schork, 1994). In clinical practice and epidemiological research, VTE events are typically categorized as either provoked or unprovoked (Kearon et al., 2016; Lutsey & Zakai, 2022; Rosendaal, 1999). Provoked VTE is associated with identifiable temporary or persistent clinical risk factors, such as major surgery, trauma, or immobilization (Anderson et al., 1991; Khan et al., 2021). Unprovoked VTE occurs in the absence of such clear external triggers (Kearon et al., 2016; Heit et al., 2016). This distinction is important for management, as patients with unprovoked events face a higher risk of long-term recurrence after their anticoagulant therapy has ended (Baglin et al., 2003; Khan et al., 2021; Lutsey & Zakai, 2022).

The genetic contribution to VTE susceptibility is substantial, with heritability estimates from family and twin studies ranging from 30% to 60% (Heit et al., 2004; Lutsey & Zakai, 2022; Zöller et al., 2021). Inherited thrombophilia refers to genetic variations that lead to a prothrombotic state, primarily through loss-of-function in natural anticoagulants or gain-of-function in procoagulant factors (Martinelli et al., 2014; Zöller et al., 2020).

Deficiencies in the natural coagulation inhibitors, antithrombin, protein C, and protein S, are the most potent but also the rarest inherited defects, occurring in less than 1% of the general population (Comp & Esmon, 1984; Dahlbäck et al., 1993; Svensson & Dahlbäck, 1994; Griffin et al., 1981; Mannucci & Franchini, 2015; Zöller et al., 2020). These deficiencies can increase the risk of a first VTE by 2- to 50-fold depending on genotype, age, and clinical presentation (Allart et al., 1993; Lijfering et al., 2010; Martinelli et al., 2014). The most prevalent genetic variants in Caucasian populations are FVL and the prothrombin G20210A mutation (Bertina et al., 1994; Poort et al., 1996; Mannucci & Franchini, 2015; Svensson et al., 1997; Zöller et al., 2020). FVL causes resistance to APC, increasing the risk of VTE approximately 5-fold in heterozygotes and up to 50-fold or higher in homozygotes (Bertina et al., 1994; Zöller & Dahlbäck, 1994; Lijfering et al., 2010; Zöller et al., 2020). The prothrombin G20210A mutation results in elevated plasma prothrombin levels and is associated with a 2- to 4-fold increase in risk (Poort et al., 1996; Lijfering et al., 2010; Mannucci & Franchini, 2015).

Large-scale GWAS and cross-ancestry meta-analyses have expanded the genetics of VTE, identifying more than 130 independent risk loci (Thibord et al., 2022). While traditional genetic risk factors are primarily localized to the coagulation cascade, these findings show new pathways, such as those involving platelet biology and blood cell traits (Ghouse et al., 2023; Lindström et al., 2019; Thibord et al., 2022). The development of polygenic risk scores has made it possible to identify individuals who exhibit a VTE risk comparable to carriers of monogenic mutations, such as FVL and the prothrombin G20210A variant (Ghouse et al., 2023; Klarin et al., 2019).

Recent studies have identified C1-inhibitor deficiency as a novel and rare hereditary thrombophilia (Sundler Björkman et al., 2024). Nationwide family data indicate that patients with hereditary angioedema exhibit a 2.5-fold increased hazard for VTE (Sundler Björkman et al., 2024). Population-scale genomic data indicate that deleterious *SERPING1* variants are rare, occurring in approximately 1 in 10,000 individuals (Rodriguez Espada et al., 2026).

Age is an independent risk factor for VTE, with the incidence being exceptionally low in children and rising exponentially with advancing age, particularly after age of 60 (Hansson et al., 1997; Lijfering et al., 2010; Martinelli et al., 2014; Silverstein et al., 1998). This increase may be due to the cumulative effect of vessel wall degradation, decreased mobility, and an increased prevalence of comorbid conditions (Heit et al., 2016; Rosendaal, 1999; Turetz et al., 2018; White, 2003).

Surgery and trauma are provoking factors, especially major orthopedic procedures such as hip or knee arthroplasty, and neurosurgery (Khan et al., 2021; Lutsey & Zakai, 2022; Sevitt & Gallagher, 1959). The risk is driven by tissue trauma, postoperative inflammation, and the necessity of perioperative immobilization (Lijfering et al., 2010; Turetz et al., 2018).

Pregnancy and the postpartum period represent periods of high risk due to physiological hypercoagulability and mechanical venous obstruction (Brenner, 2004; Lutsey & Zakai, 2022; Turetz et al., 2018). The risk is 4- to 5-fold higher during pregnancy and peaks during the first 6 weeks postpartum, when the hazard can be up to 20 times higher than in nonpregnant women (Lutsey & Zakai, 2022; Martinelli et al., 2014).

Hormonal therapy, including combined oral contraceptives and hormone replacement therapy (HRT), significantly increases the risk of VTE (Lijfering et al., 2010; Martinelli et al., 2014; Sartwell et al., 1969). Combined oral contraceptives can increase the relative risk 4- to 7 times (Lijfering et al., 2010; Turetz et al., 2018; Sartwell et al., 1969).

Immobilization and venous stasis, whether due to prolonged bed rest, lower-limb casting, or long-distance travel (>4–6 hours) (Cruickshank et al., 1988; Lapostolle et al., 2001), are risk factors for VTE (Heit et al., 2016; Khan et al., 2021; Lijfering

et al., 2010). Hospitalization for an acute medical illness itself carries a high risk of VTE (Anderson et al., 1991), often combining an underlying inflammatory state with enforced immobility (Lutsey & Zakai, 2022; Turetz et al., 2018).

Malignancy is a major driver of VTE, accounting for approximately 20% of incident cases (Baylis et al., 2021; Timp et al., 2013). Trousseau's syndrome characterizes the clinical association between malignancy and a hypercoagulable state, manifested by the occurrence of VTE as a complication in patients with cancer. The phenomenon was first described in 1865 by the French internist Armand Trousseau, who documented the development of thrombosis in patients with underlying gastric cancer (Donati, 2009). Active cancer increases the risk of VTE through various mechanisms (Blom et al., 2005), including the release of procoagulant particles and chemotherapy side effects (Heit et al., 2016; Khan et al., 2021; Khorana et al., 2008).

Cardiometabolic diseases, such as heart failure (Tang et al., 2016), myocardial infarction, and atherosclerosis (Prandoni et al., 2003), have been linked to VTE via shared mechanisms of systemic inflammation and altered blood flow (Ageno et al., 2008; Gregson et al., 2019). While hypertension and diabetes often show an association with VTE, this relationship is frequently mediated by obesity (Gregson et al., 2019).

Autoimmune and inflammatory disorders, including SLE and IBD, are associated with a higher incidence of VTE (Zöller et al., 2012) due to chronic immune activation (Colling et al., 2021; Ding et al., 2023).

Obesity exhibits a clear dose-response relationship with VTE, with individuals with a BMI >35 kg/m² experiencing a 6-fold higher risk compared to those of normal weight (Gregson et al., 2019; Lutsey & Zakai, 2022). Anthropometric obesity measures exhibit a clearer dose-dependent association with incident VTE in women than in men, particularly in the absence of prior cardiovascular disease or malignancy (Brink et al., 2023; Brodin et al., 2026). Obesity contributes to both chronic low-grade inflammation and increased intra-abdominal pressure, disturbing venous return (Lijfering et al., 2010; Lutsey & Zakai, 2022).

Prior VTE is the strongest predictor of future events, indicating that for many individuals, VTE is a chronic condition with episodic events (Heit et al., 2016; Khan et al., 2021). Other recognized risk factors include smoking, taller height, and air pollution (Lijfering et al., 2010; Lutsey & Zakai, 2022; Zöller et al., 2017a).

Treatment and Secondary Prevention

VTE management is often divided into initial, primary (3–6 months), and secondary prevention phases (Ortel et al., 2020; Stevens et al., 2021). Anticoagulation remains the main therapy for confirmed VTE events (Khan et al., 2021). Guidelines prioritize direct oral anticoagulants (DOACs)—including apixaban, rivaroxaban,

edoxaban, and dabigatran—over vitamin K antagonists (VKAs) for most patients (Konstantinides et al., 2019; Ortel et al., 2020; Stevens et al., 2021). This shift is supported by large trials, which demonstrate that DOACs offer noninferior efficacy with a superior safety profile regarding major bleeding (Agnelli et al., 2013; Hokusai-VTE Investigators, 2013). A study in 2026 showed significantly less bleeding with apixaban compared to rivaroxaban in acute VTE when treated for three months (Castellucci et al., 2026). VKAs remain indicated for specific subgroups, such as patients with antiphospholipid syndrome or severe renal insufficiency (Ortel et al., 2020; Stevens et al., 2021).

The duration of treatment is primarily guided by whether the event was provoked or unprovoked (Ortel et al., 2020). Provoked VTE typically requires only 3–6 months of anticoagulation treatment (Khan et al., 2021; Konstantinides et al., 2019; Stevens et al., 2021). Meta-analyses of individual patient data have confirmed that while the short-term risk is low after provoked events, the risk of recurrence remains high in unprovoked cases (Boutitie et al., 2011). Patients with unprovoked VTE face high long-term recurrence risks, making continuing anticoagulation the standard recommendation provided the bleeding risk is not too high (Khan et al., 2021; Ortel et al., 2020). For these patients, reduced-dose regimens have been validated as effective for secondary prevention (Weitz et al., 2017).

There are treatment challenges in multimorbid patients, as these individuals often have lower anticoagulation quality and increased adverse events (Lange et al., 2019; Marcucci et al., 2013). Prospective cohort data indicate that multimorbid patients spend significantly less time within the therapeutic international normalized range (INR) when treated with VKAs (Lange et al., 2019). Bleeding risk is frequently elevated due to advanced age, chronic renal impairment, and anemia (Khan et al., 2021; Ortel et al., 2020). Furthermore, polypharmacy with risk of drug-drug interactions, which can alter DOAC concentrations (Ortel et al., 2020; Stevens et al., 2021). Individualized risk assessment is important to balance VTE protection against the risk of life-threatening bleeding (Lange et al., 2019).

While individual risk factors for VTE are well established, the cumulative impact of multimorbidity regarding VTE risk has not been fully explored, primarily because medical research and clinical practice have historically been organized around a single-disease perspective rather than the total disease burden.

Aims

The overall aim of this thesis was to characterize multimorbidity as a risk factor for VTE.

- Study I: To investigate the association between multimorbidity severity (i.e., the number of NCDs) and VTE, and to determine potential shared familial susceptibility.
- Study II: To examine if nonrandom multimorbidity disease clusters are associated with VTE.
- Study III: To examine the association between multimorbidity and its severity with the risk of incident VTE.
- Study IV: To investigate the association between primary care-diagnosed multimorbidity and its severity with the risk of incident VTE.

Methods

Study Methods

Study Design

The research presented in this thesis is based on a series of nationwide register-based studies designed to explore the association between multimorbidity and VTE (Ahrén et al., 2023, 2024, 2025, 2026). The overarching methodology went from hypothesis-generating extended cross-sectional designs to longitudinal cohort studies employing a landmark approach to establish temporal associations, reduce the risk of reverse causation, and immortal-time bias (Anderson et al., 1983; Dafni, 2011).

Studies I and II were designed as extended cross-sectional studies covering the period 1997–2015 (Ahrén et al., 2023, 2024). Study I focused on the association between multimorbidity severity and VTE risk, incorporating a family study design to assess shared familial susceptibility (Ahrén et al., 2023). Study II used a PCA and factor analysis to identify specific disease clusters associated with VTE (Ahrén et al., 2024).

Studies III and IV moved to a prospective cohort design using a landmark approach. Study III utilized three landmarks (2002, 2007, and 2012) with follow-up through 2015 (Ahrén et al., 2025). Study IV used two landmarks (2010 and 2015) with follow-up extending to 2018 (Ahrén et al., 2026).

Data sources / Registers

Data were linked across several Swedish national health and administrative registers using the unique personal identity number (PIN), which was pseudonymized by Statistics Sweden to ensure participant confidentiality. The following registers were utilized:

- National Patient Register (NPR): Provided data on hospital discharge diagnoses (nationwide since 1987) and outpatient specialist care (since 2001) (Ludvigsson et al., 2011).
- Total Population Register (TPR): Supplied demographic information, including sex, year of birth, place of residence, migration data, and educational attainment (Ludvigsson et al., 2016).

- Swedish Cause of Death Register: Provided the date and cause of death (Johansson & Westerling, 2000).
- Swedish Multigeneration Register: Enabled the identification of familial relationships (e.g., parents, siblings, and cousins) to investigate familial aggregation and genetic susceptibility (Ekbom, 2011).
- National Prescribed Drug Register: (Used in Study IV) Provided data on dispensed medications, specifically to identify the use of anticoagulants and hormonal therapies (Wallerstedt et al., 2016).
- Primary Care Data: (Used in Study IV) Provided diagnoses from general practice (Sundqvist et al., 2022).

Study population

The study populations were defined based on residency in Sweden and linkage to national registers. In Studies I, II, and III, the population consisted of 2,694,442 Swedish-born individuals born between 1947 and 2005, restricting these cohorts to individuals with Swedish-born parents (Ahrén et al., 2023, 2024, 2025).

In Study IV, the population was 8,170,329 individuals, reflecting Swedish demographics by including both Swedish-born and foreign-born residents (Ahrén et al., 2026). Exclusion criteria for the landmark cohort studies (III and IV) included a history of VTE before the start of follow-up (i.e. prevalent VTE), death, and emigration before the respective landmark baseline. Additionally, in Study IV, individuals using anticoagulants (such as DOACs or warfarin), oral contraceptives, or HRT at baseline were excluded to minimize confounding related to medication-induced VTE risk or protection in the analyses.

Exposures and outcomes

Multimorbidity was the primary exposure, defined as the co-occurrence of two or more NCDs. This was measured using a list of 45 NCDs (Zöller et al., 2023). A multimorbidity score (0, 1, 2, 3, 4, or ≥ 5) was calculated for each individual to assess the dose-response relationship of disease burden on VTE risk (Zöller et al., 2023).

In Studies II, III, and IV, individual NCDs were categorized into nine distinct disease clusters (F1–F9) using PCA followed by factor analysis with an oblique Promax rotation (Zöller et al., 2023). These clusters comprised:

- F1 (Cardiometabolic diseases): Hypertension, heart failure, coronary heart disease, diabetes, obesity, atrial fibrillation, gout, atherosclerosis, and renal disease.
- F2 (Psychiatric diseases): Affective disorders, anxiety, psychoactive substance misuse, alcohol misuse disorders, anorexia or bulimia, and schizophrenia disorders.

- F3 (Digestive system diseases): IBD, liver disease, pancreatic disease, and ulcers.
- F4 (Neurological/Cancer): Epilepsy, blindness and poor vision, cerebrovascular disease, cancer, and hearing impairment or loss.
- F5 (Connective tissue/autoimmune): Connective tissue disease, osteoporosis, thyroid disorders, and psoriasis.
- F6 (Prostate/Musculoskeletal): Prostate disease, arthrosis, painful back condition, diverticular disease of the intestine, and chronic sinusitis.
- F7 (Neurodegenerative/bowel): Bronchiectasis, Parkinson's disease, glaucoma, learning disability, and IBS.
- F8 (Respiratory/Atopic): Asthma, dermatitis and eczema, constipation, COPD, and migraine.
- F9 (Neurodegenerative): Multiple sclerosis and dementia.
- The primary outcome was incident VTE, defined as PE or DVT, identified using ICD-10 codes I26 and I80 (excluding I80.0).

Statistical analysis

Different statistical methods were applied to accommodate the study designs. In Studies I and II, logistic regression was used to estimate odds ratios (ORs) with 95% confidence intervals (CIs) (Cox, 1958; Ahrens & Pigeot, 2014). To address the familial risks in Study I, a double-entry approach was utilized for relative pairs, and robust standard errors were calculated using the variance-covariance cluster method to account for intragroup correlation within families (DeFries & Fulker, 1985; Kohler & Rodgers, 2001). In Study II, a PCA was used to identify different disease clusters (Hotelling, 1933; Jolliffe & Cadima, 2016).

In Studies III and IV, Fine and Gray proportional hazards models were employed to estimate hazard ratios (HRs) or subdistribution hazard ratios (subHRs). This method accounts for competing risks, such as death and emigration, which may prevent the occurrence of VTE (Fine & Gray, 1999). Cumulative incidence functions (CIF) and Kaplan-Meier survival curves were generated to visualize VTE-free survival time across multimorbidity scores (Kaplan & Meier, 1958; Satagopan et al., 2004).

Models were adjusted for sociodemographic confounders, including sex, year of birth, and educational attainment (Hill, 1965; Marmot et al., 1978). Studies I, II and IV also adjusted for region of birth. Study IV used the most extensive adjustment model, including VTE in siblings, and inherited thrombophilia's: FVL mutation, deficiencies in antithrombin, protein C, or protein S. Also, human immunodeficiency virus, chronic viral hepatitis B, chronic viral hepatitis C. Interaction analyses were also performed in Study IV to examine the modifying

effects of sex and country of birth on the association between multimorbidity and VTE.

Statistical Methods

Registers

The foundation of register-based research in Sweden is the unique PIN assigned to all residents since 1947 (Ludvigsson et al., 2009). The PIN consists of an individual's birth date, a three-digit birth number that is sex-specific, and a check digit (Ludvigsson et al., 2009; Lunde et al., 1980). This enables the linkage of individual-level data across various nationwide health and administrative registers (Ludvigsson et al., 2009). The PIN provides virtually 100% coverage of the Swedish healthcare system and tracing medical records and referrals over time (Ludvigsson et al., 2009). To ensure confidentiality in research, the PIN is replaced with a pseudonymized serial number by Statistics Sweden before data delivery (Ludvigsson et al., 2016).

The Total Population Register, which has been maintained by Statistics Sweden since 1968, serves as the basis for identifying study cohorts and calculating person-years at risk (Ludvigsson et al., 2016). The TPR contains demographic variables, including age, sex, place of residence, civil status, and dates of immigration or emigration (Ludvigsson et al., 2016). Coverage is high, with nearly 100% of births and deaths reported within 30 days (Ludvigsson et al., 2016).

To investigate familial aggregation and heritability, the Swedish Multigeneration Register is linked to the study population (Ekbom, 2011). This register contains links for more than 9 million individuals born since 1932 who were alive in 1961 (Ekbom, 2011). Information on biological mothers is found for 97% of index persons, while information on fathers is found for 95% (Ekbom, 2011). The register is used to construct pedigrees involving siblings, half-siblings, and cousins (Ekbom, 2011).

Clinical outcomes and diseases are obtained from the NPR and the Swedish Cause of Death Register (Ludvigsson et al., 2011). The NPR includes hospital discharge diagnoses from 1964 and specialized outpatient hospital diagnoses since 2001 (Ludvigsson et al., 2011). The inpatient component has had nationwide coverage since 1987, and diagnoses are coded according to the ICD system (Ludvigsson et al., 2011). The general validity of the NPR is high, with a median positive predictive value of 84% for diagnostic codes (Everhov et al., 2025). The accuracy for VTE has been validated at approximately 90%–95% (Andersson et al., 2022; Ludvigsson et al., 2011).

The Swedish Cause of Death Register provides nationwide data on the date and underlying cause of death since 1961, ensuring complete follow-up for mortality (Johansson & Westerling, 2000).

Primary care data are incorporated to capture chronic conditions managed outside the hospital setting. These data contain KSH97-P diagnoses based on ICD-10 diagnoses from primary care physician visits and cover approximately 90% of the Swedish population (Socialstyrelsen, 1997; Sundqvist et al., 2022). Linking primary care data to hospital registers provides a more comprehensive multimorbidity profile for each individual, as many chronic NCDs are managed in primary care (Finley et al., 2018). The use of these combined registers provides a high degree of coverage and validity, representing a major strength of the study design.

Logistic Regression and Effect Estimates

Logistic regression is a standard statistical method used to model the relationship between a binary outcome and one or more explanatory variables (Cox, 1958; Ahrens & Pigeot, 2014). The model estimates the probability of the event occurring by applying a logistic function to a linear combination of predictors (Walker & Duncan, 1967). Effect estimates are typically expressed as ORs, which quantify the relative odds of the outcome in an exposed group compared to a reference group (Cornfield, 1951). These estimates are accompanied by 95% CIs to provide a measure of the precision of the estimated effect (Ahrens & Pigeot, 2014).

Double Entry Approach

The double entry approach is a data management technique used in familial aggregation and genetic studies to deal with the uncertainty of proband assignment in relative pairs (Kohler & Rodgers, 2001). In this procedure, each member of a pair is entered into the dataset twice, once as the index individual and once as the relative (Kohler & Rodgers, 2001). Although this method ensures that regression estimates for heritability remain consistent, it artificially inflates the sample size and leads to biased standard errors (DeFries & Fulker, 1985; Kohler & Rodgers, 2001). To provide valid statistical inference, robust standard errors must be calculated using the variance-covariance cluster method (Kohler & Rodgers, 2001; White, 1980), treating each family as an independent cluster (Kohler & Rodgers, 2001).

Landmark Analysis

Landmark analysis is a methodological approach designed to compare time-to-event outcomes between groups defined during the follow-up period (Anderson et al., 1983; Dafni, 2011). Designating a fixed "landmark" time point and analyzing only those participants who have survived event-free until that point ensures a stable temporal ordering between exposure and outcome (Anderson et al., 1983; Dafni, 2011). Results are interpreted as conditional probabilities or hazards based on group membership at the landmark time (Anderson et al., 1983; Morgan, 2019).

Competing Events and Hazard Ratios

In longitudinal research, competing risks occur when individuals experience events that prevent the occurrence of the primary event of interest (Prentice et al., 1978; Satagopan et al., 2004). Standard survival models, such as the Cox proportional hazards model (Cox, 1972), may result in biased results if these competing events are treated as independent censoring (Prentice et al., 1978; Kim, 2007). To address this, the Fine and Gray proportional hazards model is utilized to estimate subHRs (Fine & Gray, 1999; Gray, 1988). This model is particularly useful for risk prediction, as it keeps individuals who have experienced a competing event within the risk set for the primary outcome (Fine & Gray, 1999).

Cumulative Incidence and Kaplan-Meier

The Kaplan-Meier estimator is a nonparametric method used to estimate the survival function or the probability of remaining event-free over time (Kaplan & Meier, 1958; Satagopan et al., 2004). However, in the presence of competing risks, the Kaplan-Meier method tends to overestimate absolute risk because it assumes that censored individuals have the same future hazard as those remaining in the study (Kim, 2007). The CIF provides an unbiased estimate of event probability by explicitly accounting for the probability of experiencing competing events first (Gray, 1988; Satagopan et al., 2004). While Kaplan-Meier method focuses on the probability of not failing, the CIF accounts for the probability of failing due to a specific cause (Gray, 1988; Kim, 2007).

Incidence Rate and Incidence Rate Ratios

Incidence rates quantify the frequency of new events occurring in a population over a specific period, typically expressed as cases per 1000 person-years (Miettinen, 1976; Rossello & González-Del-Hoyo, 2022). This measure represents the absolute burden of disease relative to the total time contributed by participants at risk (Rossello & González-Del-Hoyo, 2022). The incidence rate ratio (IRR) is a relative measure that compares the rate of events between two different strata (Rossello & González-Del-Hoyo, 2022). These metrics are tools to understand both the velocity and the relative risk of disease occurrence within a cohort (Miettinen 1976; Rossello & González-Del-Hoyo, 2022).

Log-log Curves and Proportional Hazards

The proportional hazards assumption is a requirement for Cox-type survival models, stating that the HR between groups remains constant over the observation period (Cox 1972; Rossello & González-Del-Hoyo, 2022). This assumption is assessed through visual inspection of log-log survival function curves (Rossello & González-Del-Hoyo, 2022). If the proportional hazards assumption holds, the log-log plots for different exposure groups should remain parallel and not cross over time (Rossello & González-Del-Hoyo, 2022). Crossover in these plots indicates a time-dependent

effect, necessitating stratified or alternative modeling strategies (Cox, 1972; Rossello & González-Del-Hoyo, 2022).

Principal Component Analysis and Promax Rotation

PCA is a data reduction technique used to simplify complex datasets with many correlated predictor variables (Hotelling, 1933; Jolliffe & Cadima, 2016). PCA transforms correlated original variables into a smaller set of uncorrelated composite variables, called principal components, which successively maximize the variance captured from the data (Sainani, 2014). To enhance the clinical interpretability of these components, rotation methods are applied to align variables more strongly with specific factors (Jolliffe & Cadima, 2016; Thurstone, 1947). Promax rotation is an oblique rotation method that allows for correlation between the identified components (Tinkler, 1972).

Confounding and Adjustment Strategies

Confounder selection is guided by established clinical knowledge and previous epidemiological research regarding associations with both the exposure and the outcome (Hill, 1965; Marmot et al., 1978). Multivariate adjustment strategies are important to account for potential bias and isolate independent associations (Winkleby et al., 1992). Standard models include adjustments for year of birth to account for cohort effects, region of birth for geographical variations, and sex (Marmot et al., 1978). Level of education is frequently utilized as a surrogate measure for SES and lifestyle-related factors, such as smoking and physical activity, which are often unavailable in register-based data (Winkleby et al., 1992).

Sex-specific and Age-specific Analyses

To explore potential heterogeneity in risk estimates, stratified analyses are conducted based on sex and age (Marmot et al., 1978; Rossello & González-Del-Hoyo, 2022). Sex-specific analyses evaluate whether the impact of a risk factor varies between biological males and females (Winkleby et al., 1992). Age-specific analyses, often stratified by birth year quartiles, allow for the assessment of whether the relative importance of a risk factor changes across different life stages (Marmot et al., 1978; Rossello & González-Del-Hoyo, 2022). These stratifications are important for identifying high-risk subgroups and ensuring the reliability of primary findings (Marmot et al., 1984; Rossello & González-Del-Hoyo, 2022).

Sensitivity Analyses

Sensitivity analyses are performed to assess the robustness of the primary findings and the impact of potential biases or alternative model specifications (Dafni, 2011; Hill, 1965). These may include interaction analyses to identify effect modification or models excluding individuals using specific medications, such as anticoagulants, that might interfere with the outcome (Dafni, 2011). Testing different landmark time

points or model assumptions further ensures that the observed associations are reliable (Anderson et al., 1983; Morgan, 2019).

Statistical Software

All statistical computations and data management procedures were performed using Stata version 16.1 (StataCorp LLC, College Station, TX, USA).

Ethical Considerations

The study was conducted in accordance with the ethical principles for medical research and was approved by the Swedish Ethical Review Authority (formerly the Regional Ethical Review Board in Lund; reference number 2012/795 and subsequent amendments). This research utilized secondary data obtained from several nationwide Swedish registers.

Linkage of these datasets was performed by Statistics Sweden and the National Board of Health and Welfare using the unique Swedish PIN. To ensure the confidentiality and privacy of the participants, the PINs were replaced with coded serial numbers, which resulted in a pseudonymized dataset for the researchers. Consequently, the research team had no access to directly identifiable personal information, and there was no risk of backward identification.

In accordance with Swedish legislation and the established norms for register-based research, individual informed consent was not required. This is based on the premise that the research serves a significant public interest, is conducted on pseudonymized data, and has been approved by an ethical review board. Obtaining informed consent from each individual for a study population involving millions of individuals is also considered impractical and would likely introduce selection bias, thereby compromising the statistical power and generalizability of the results.

All data were stored and analyzed in secure environments on remote, locked servers to ensure compliance with relevant data protection regulations. The potential risk to individual participants was considered minimal, as all findings are presented exclusively at the group level. The benefits of gaining improved knowledge regarding the risk factors and predictors for VTE were judged to outweigh the minimal risks associated with the use of pseudonymized register data.

Results

Study I

To investigate the association between multimorbidity severity (i.e., the number of NCDs) and VTE, and to determine potential shared familial susceptibility. The study population consisted of 2,694,442 unique Swedish-born individuals. At the end of the follow-up period in 2015, the median age was 32 years (IQR 22–43). A total of 16.36% (n=440,742) were diagnosed with multimorbidity, defined as the presence of two or more of the 45 NCDs studied. A sex difference was observed: females consisted of 48.73% of the total population but made up 57.61% of the multimorbid group. The prevalence of multimorbidity increased with age; individuals with a multimorbidity score of 5 or more had a median age of 42 years (IQR 31–50) compared to 31 years (IQR 22–42) for those with a score of 0. There was an inverse relationship between education and multimorbidity, where 31.32% of those with a score <2 had at least 12 years of education, but only 19.32% of those with a score of 5 or more.

A total of 16,099 cases of VTE were identified during the study period (1997–2015). The frequency of VTE was 1.58% in the multimorbid group compared to 0.40% in individuals with one or no diagnoses. In the unadjusted model (Model 1), the OR for VTE in individuals with multimorbidity was 3.96 (95% CI: 3.84–4.09). After adjusting for birth year, sex, region of birth, and educational attainment (Model 2), the OR was 3.16 (95% CI: 3.06–3.27).

The association was stronger in males, adjusted OR 3.45 (95% CI: 3.29–3.62) than in females, adjusted OR 2.91 (95% CI: 2.79–3.04). Stratification by age quartiles (IQR1–4) demonstrated that the association was stable across different quartiles. For the oldest quartile (born 1947–1972), the adjusted OR was 3.14 (95% CI: 3.01–3.29), while the youngest quartile (born 1993–2005) had an adjusted OR of 3.07 (95% CI: 2.56–3.7).

There was a significant and consistent dose-response relationship between the number of NCDs and the risk of VTE. Compared to individuals with no diseases (score 0), the adjusted ORs (Model 2) increased as shown in Table 1.

Table 1. Odds ratio for venous thromboembolism (VTE) according to multimorbidity score (0 to ≥5). Odds ratios (ORs) with 95% confidence interval (CI) for multimorbidity scores. Reference with no diseases (score=0).

	All (n=2694442)		
	OR (95% CI)		
Multimorbidity score	No VTE	VTE	Model 2
Score 0	1611205	5008	1[Reference]
Score 1	633379	4108	1.94 (1.86–2.02)
Score 2	251558	2652	2.93 (2.80–3.08)
Score 3	102969	1665	4.07 (3.85–4.31)
Score 4	44522	1063	5.46 (5.10–5.85)
Score ≥5	34710	1603	9.08 (8.56–9.64)
Abbreviations: CI, confidence interval; OR, odds ratio; VTE, venous thromboembolism. Model 2 is an adjusted (multivariable) model, with adjustments for sex, year of birth, county, and educational attainment.			
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The analysis of familial datasets (twins, siblings, half-siblings, and cousins) revealed significant but generally weak familial associations between multimorbidity in relatives and VTE. In the adjusted model, the risk of VTE was higher if a relative had multimorbidity:

- Twins: OR 1.89 (95% CI: 1.17–3.05)
- Full siblings: OR 1.18 (95% CI: 1.12–1.24)
- Half-siblings: OR 1.10 (95% CI: 1.03–1.18)
- Cousins: OR 1.07 (95% CI: 1.04–1.10)

The risk further increased with the severity of the relative's multimorbidity. For example, having a twin with a multimorbidity score of 5 or more was associated with an adjusted OR of 3.98 (95% CI: 1.69–9.39) for VTE in the index person. Study I established a dose-graded association between multimorbidity and VTE.

Study II

To examine whether nonrandom multimorbidity disease clusters are associated with VTE. It was the same study population as in Study I. Each of the 45 NCDs included in the multimorbidity index was tested individually for an association with VTE. The four strongest individual disease associations identified were for atherosclerosis OR 7.66 (95% CI: 7.02–8.35), heart failure OR 5.02 (95% CI: 4.47–5.63), bronchiectasis OR 4.31 (95% CI: 2.77–6.69), and cancer OR 3.76 (95% CI: 3.57–3.95).

The 45 NCDs were grouped into nine disease clusters (F1–F9). These clusters represented clinically relevant patterns: F1 (Cardiometabolic diseases), F2 (Psychiatric diseases), F3 (Digestive system diseases), F4 (Neurological/Cancer), F5 (Connective tissue/autoimmune), F6 (Prostate/Musculoskeletal), F7 (Neurodegenerative/Bowel), F8 (Respiratory/Atopic), and F9 (Neurodegenerative). Seven of these nine clusters (F1–F6 and F8) demonstrated significant associations with VTE.

The highest adjusted ORs (Model 2) for multimorbid individuals within specific clusters were observed in:

- F4 (epilepsy, cancer, blindness and poor vision, cerebrovascular disease, cancer, and hearing impairment or loss): 5.65 (95% CI: 5.14–6.21).
- F3 (IBD, liver disease, pancreatic disease, and ulcers): 4.35 (95% CI: 3.63–5.22).
- F1 (hypertension, heart failure, coronary heart disease, diabetes, obesity, atrial fibrillation, gout, atherosclerosis, and renal disease): 3.44 (95% CI: 3.24–3.65).
- F5 (connective tissue disease, osteoporosis, thyroid disorders, and psoriasis): 3.32 (95% CI: 2.87–3.84).
- F8 (asthma, dermatitis and eczema, constipation, COPD, and migraine): 3.08 (95% CI: 2.85–3.33).
- F6 (prostate disease, arthrosis, painful back condition, diverticular disease of the intestine, and chronic sinusitis): 2.56 (95% CI: 2.34–2.80).
- F2 (affective disorders, anxiety, psychoactive substance misuse, alcohol misuse disorders, anorexia or bulimia, and schizophrenia disorders): 2.25 (95% CI: 2.14–2.37).

Cluster F7 (bronchiectasis, Parkinson’s disease, glaucoma, learning disability, and IBS) OR 0.90 (95% CI: 0.22–3.65) and F9 (multiple sclerosis and dementia) (not applicable due to few cases) did not show a significant association with VTE.

An increase in VTE risk was observed as the number of diseases within specific clusters increased. In the cardiometabolic cluster (F1), the adjusted OR for 1 disease was 2.92 (95% CI: 2.80–3.04), rising to 8.17 (95% CI: 6.32–10.55) for 5 or more diseases. In the psychiatric cluster (F2), the adjusted OR increased from 1.73 (95% CI: 1.65–1.82) for 1 disease to 6.31 (95% CI: 4.34–9.17) for 5 or more diseases. For the digestive system cluster (F3), a score of 4 had an adjusted OR of 15.5 (95% CI: 3.33–68.88). Similarly, in the neurological/cancer cluster (F4), the risk for individuals with 5 or more diseases was exceptionally high with an adjusted OR, 20.74, (95% CI: 2.10–204.30), although with a very wide CI due to the small number of cases. This study identified specific, nonrandom disease clusters where VTE risk increases significantly with the number of conditions within each cluster.

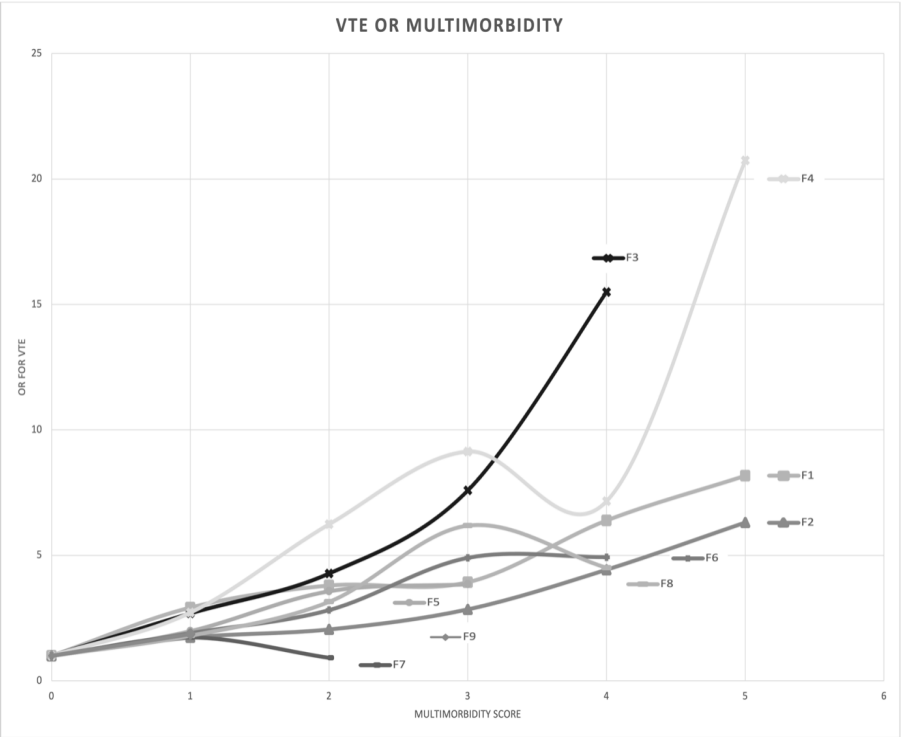


Figure 1. Odds ratio (OR) for venous thromboembolism (VTE) with increasing multimorbidity score for disease cluster F1–F9, adjusted (multivariable) model, with adjustments for sex, year of birth, region of birth, and educational attainment. Reproduced from Ahrén et al., 2024, licensed under CC BY 4.0.

Study III

To examine the association between multimorbidity and its severity with the risk of incident VTE. This cohort study used a landmark approach to analyze incident VTE across three baseline timepoints (Landmarks 1, 2, and 3). For Landmark 1 (L1), 2,694,442 individuals were initially included, of whom 174,437 were excluded due to prevalent VTE ($n=1,551$), death ($n=4,162$), emigration ($n=6,601$), or being born after the baseline ($n=162,123$). This resulted in a final cohort of 2,520,005 individuals for the L1 analysis. Multimorbidity at L1 baseline was present in 0.90% ($n=22,665$) of the population. Females comprised 53.73% of the multimorbid group at L1, and this proportion increased to 58.99% in the group with a multimorbidity score of ≥ 5 .

During the 14-year follow-up for L1, a total of 14,525 incident VTE events occurred (0.58%). The frequency of VTE events was higher in the multimorbid group (1.96%) compared to nonmultimorbid individuals (0.56%). The IR for VTE in the multimorbid group was 1.48 per 1,000 person-years (95% CI: 1.34–1.61), compared to 0.41 per 1,000 person-years (95% CI: 0.4–0.41) in those with a score < 2 .

In the multivariable model adjusted for sex, birth year, and education, multimorbidity was a predictor of incident VTE across all landmarks. The adjusted HR was 2.47 (95% CI: 2.24–2.72) in L1, 2.23 (95% CI: 2.11–2.36) in L2, and 2.16 (95% CI: 2.03–2.29) in Landmark 3.

The risk for incident VTE in L1 increased in a dose-graded pattern with multimorbidity severity. Compared to individuals with no diseases (score 0), the adjusted HRs were:

- One disease (score 1): 1.76 (95% CI: 1.67–1.86)
- Two diseases (score 2): 2.38 (95% CI: 2.12–2.66)
- Three diseases (score 3): 3.06 (95% CI: 2.48–3.77)
- Four diseases (score 4): 4.07 (95% CI: 2.87–5.77)
- Five or more diseases (score ≥ 5): 4.29 (95% CI: 2.53–7.28)

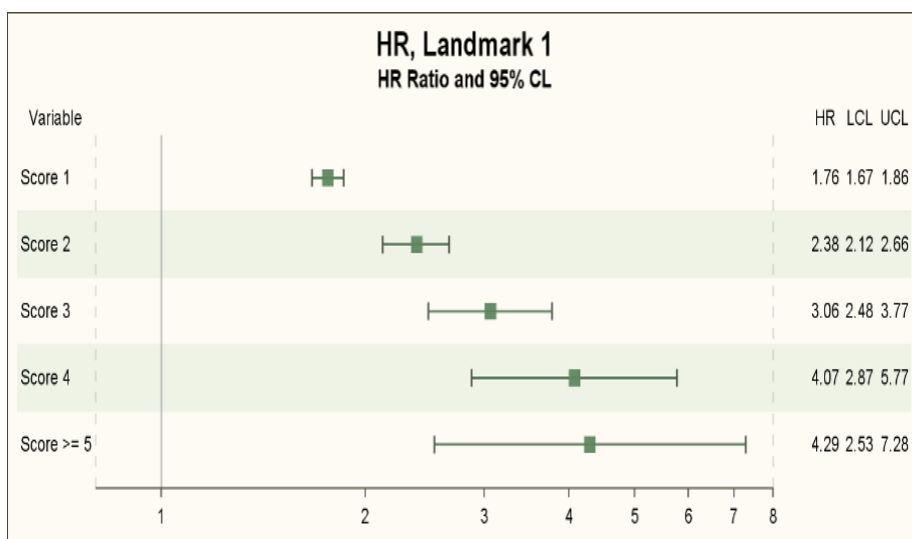


Figure 2. Forrest plot for Hazard Ratio (HR) for venous thromboembolism in landmark 1 according to multimorbidity score 1–≥5. LCL, 95% lower confidence limit; UCL, 95% upper confidence limit; CL, 95% confidence limits, CL. Reference was no disease (score=0). Reproduced from Ahrén et al., 2025, licensed under CC BY 4.0.

Seven clusters remained significant predictors of incident VTE in the L1 analysis. The cardiometabolic cluster (F1) showed an adjusted HR of 2.54 (95% CI: 1.90–3.40), and the psychiatric cluster (F2) had an adjusted HR of 2.37 (95% CI: 2.01–2.80). For individuals with a severity score of ≥5 in the F1 cluster, the adjusted HR for incident VTE was 13.11 (95% CI: 1.55–110.80), while a similar severity score in the F2 cluster had an adjusted HR of 8.69 (95% CI: 1.23–60.12). This longitudinal landmark study confirmed that multimorbidity is an independent, dose-graded predictor of incident VTE, with consistent risk across multiple follow-up periods.

Study IV

To investigate the association between primary care-diagnosed multimorbidity and its severity with the risk of incident VTE. In the Landmark 2 (L2) cohort (baseline 2015), a total of 8,170,329 individuals were included. The prevalence of primary care-diagnosed multimorbidity was 26.72% (n=2,183,236). Multimorbidity was more common in females (30.27%) than in males (24.06%). Multimorbid individuals were substantially older at the end of the study, with a median age of 60 years (IQR 44–74) compared to 34 years (IQR 18–52) for nonmultimorbid individuals. Educational level was lower in the multimorbid group, with 31.36% having at least 12 years of education compared to 46.32% in the group with one or no diseases.

During the four-year follow-up, 55,211 incident VTE events were recorded (0.68% of the total population). Among multimorbid individuals, 1.42% experienced a VTE event, compared to 0.41% in those without multimorbidity. The IR for VTE was 3.71 per 1,000 person-years (95% CI: 3.67–3.76) in the multimorbid group and 1.04 per 1,000 person-years (95% CI: 1.03–1.05) in the nonmultimorbid group.

In the fully adjusted Model 3, which accounted for sociodemographic factors, as well as inherited and acquired VTE risk factors, the adjusted subHR for multimorbidity was 1.36 (95% CI: 1.34–1.39). A consistent dose-graded relationship was observed with increasing multimorbidity score:

- One disease (score 1): subHR 1.21 (95% CI: 1.18–1.24)
- Two diseases (score 2): subHR 1.36 (95% CI: 1.32–1.39)
- Three diseases (score 3): subHR 1.46 (95% CI: 1.41–1.50)
- Four diseases (score 4): subHR 1.49 (95% CI: 1.44–1.54)
- Five or more diseases (score ≥ 5): subHR 1.62 (95% CI: 1.57–1.67)

Statistically significant differences were found for sex and country of birth. The subHR for multimorbidity was higher in females, 1.45 (95% CI: 1.41–1.49), than in males, 1.30 (95% CI: 1.27–1.33). For individuals with a score of ≥ 5 , the subHR reached 1.78 (95% CI: 1.71–1.86) in females compared to 1.48 (95% CI: 1.43–1.54) in males. Regarding country of birth, the subHR was 1.33 (95% CI: 1.30–1.36) for those born in Sweden, and for those born outside Europe, it was 1.64 (95% CI: 1.52–1.78).

Seven of the nine clusters were significantly associated with incident VTE in the primary care data. The digestive system cluster (F3) demonstrated the highest risk subHR 1.80 (95% CI: 1.39–2.32), followed by the psychiatric cluster (F2) subHR 1.39 (95% CI: 1.34–1.44) and the cardiometabolic cluster (F1) subHR 1.14 (95% CI: 1.12–1.17). Findings from the primary care setting show the dose-graded

association between multimorbidity and VTE, while identifying a higher relative impact among females and foreign-born individuals.

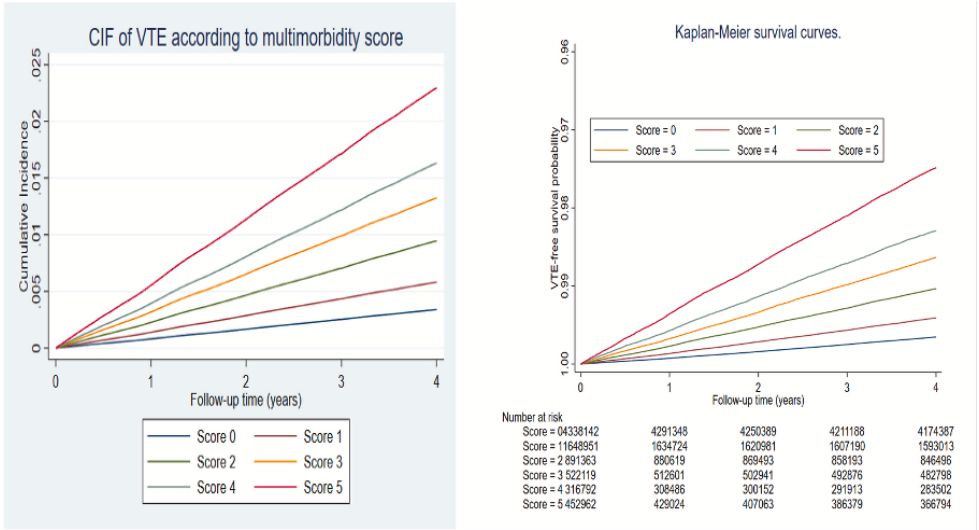


Figure 3. Cumulative incidence function (CIF) of venous thromboembolism (VTE) according to multimorbidity score (score 0–≥5) and Kaplan-Meier estimates for VTE-free survival time according to multimorbidity score (score 0–≥5) in landmark 2 with 4 years of follow-up time. Reproduced from Åhrén et al., 2026, licensed under CC BY 4.0.

Discussion

Principal Findings

The present thesis demonstrates a strong and consistent association between multimorbidity, defined as the co-occurrence of two or more NCDs, and the risk of VTE. This was seen across the four studies, from identifying cross-sectional associations to establishing multimorbidity as a dose-graded predictor for incident VTE in both hospital and primary care settings (Ahrén et al., 2023, 2024, 2025, 2026).

A consistent finding across all of the studies is the association between the total burden of NCDs and VTE risk. In our initial hypothesis-generating study, we identified an adjusted OR of 3.16 (95% CI 3.06–3.27) for individuals with multimorbidity compared to those with one or no diseases. This association was thereafter confirmed in a longitudinal cohort design using a landmark approach, which demonstrated that multimorbidity is a significant predictor of incident VTE, with an HR ranging from 2.16 (95% CI 2.03–2.29) to 2.47 (95% CI 2.24–2.72) across different follow-up periods. Furthermore, this relationship persists in the primary care setting, with a subHR of 1.36 (95% CI 1.34–1.39). While the findings were largely consistent, some divergence was observed regarding familial susceptibility; our data suggest only a weak shared familial component, indicating that the association between multimorbidity and VTE may be driven more by individual disease accumulation or shared environmental factors than by a strong common genetic background.

The risk in studies using the NPR is higher than that observed in Study IV using primary care data. This may be due to the inclusion of patients with disease severity requiring a hospital visit (Ahrén et al., 2023, 2024, 2025, 2026). The hospital setting may measure more advanced clinical patients, which may result in a stronger association with VTE compared to the primary care setting, where the inclusion of a broader and less acute and sick patient population results in lower hazard ratios (Ahrén et al., 2023, 2024, 2025, 2026).

A feature of our findings is the clear dose-graded pattern between multimorbidity severity and VTE risk. As the number of NCDs increases, the risk of VTE rises substantially. In the hospital, individuals with multimorbidity, diagnosed with 5 or

more NCDs exhibited a ninefold increased odds of VTE, OR 9.08 (95% CI 8.56–9.64), compared to those with no disease.

To further investigate this, we showed that seven of the nine distinct disease clusters were associated with VTE. The highest risks were consistently found in clusters involving cardiometabolic diseases F1 OR 3.44 (95% CI 3.24–3.65), digestive system diseases F3 OR 4.35 (95% CI 3.63–5.22), and a cluster including cancer and cerebrovascular diseases F4 OR 5.65 (95% CI 5.14–6.21). Psychiatric disorders F2 OR 2.25 (95% CI 2.14–2.37) were also a significant predictor for incident VTE.

In the primary care setting, we observed a higher relative impact on VTE risk in females, subHR 1.45 (95% CI 1.41–1.49), compared to males, subHR 1.30 (95% CI 1.27–1.33). This suggests that the cumulative burden of NCDs may interact with sex-specific biological or social factors to further elevate thrombotic risk.

Comparison with Previous Studies

The findings of this thesis, established across four nationwide studies, identify multimorbidity as a potent, independent, and dose-graded predictor of both prevalent and incident VTE. This dose-graded association was confirmed by findings in a British South Asian cohort, where VTE prevalence increased from an OR of 1.6 (95% CI 1.2–2.0) for one condition to 8.1 (95% CI 4.9–13.0) for individuals with four or more medical conditions (Magavern et al., 2023).

The observed graded association between disease burden and VTE risk aligns with the "thrombosis potential model" (Rosendaal, 1999), which conceptualizes VTE as a multicausal disease where multiple risk factors must accumulate to exceed a "thrombosis threshold". Our evidence of a multimorbidity severity gradient provides a clinical and epidemiological parallel to this theoretical framework.

Regarding specific disease groups, our finding that the cardiometabolic cluster (including hypertension, diabetes, and obesity) is a major driver of VTE risk is consistent with the meta-analysis by Ageno et al. (2008), as well as original clinical observations that established a link between atherosclerosis and VTE (Prandoni et al., 2003). Their findings showed that cardiovascular risk factors have an additive effect on VTE risk.

The observation of a substantial disease burden in VTE patients is a consistent finding across several international cohorts. For instance, the European PREFER registry (Kroep et al., 2018) reported that approximately 87% of patients with PE and 84% of those with DVT had at least one comorbidity; this high prevalence of comorbid conditions is further investigated by large-scale register-based studies in Sweden (Glise Sandblad et al., 2022; Zöller et al., 2017b) and Denmark (Bonnesen et al., 2022), as well as clinical data from US-based hospital populations (Tsai et al.,

2013). Furthermore, our identification of the psychiatric cluster as a significant predictor, OR 2.25 (95% CI 2.14–2.37), finds support in systematic reviews linking mood and anxiety disorders to increased VTE incidence (Kowal et al., 2020).

A notable inconsistency observed across the studies in this thesis concerns the relative impact of sex on the association between multimorbidity and VTE. In our initial nationwide cross-sectional study (Study I), the association was significantly stronger in males, adjusted OR 3.45 (95% CI 3.29–3.62), than in females, OR 2.91 (95% CI 2.77–3.04) (Ahrén et al., 2023). However, this shifted in the primary care setting (Study IV), where multimorbidity was found to be a more potent risk factor among females, subHR 1.45 (95% CI 1.41–1.49), compared to males, subHR 1.30 (95% CI 1.27–1.33) (Ahrén et al., 2026). This finding that multimorbidity is a dominant relative risk factor for women in primary care is in parallel alignment with the demographic distribution in the study by Barnett et al., 2012. They reported a higher prevalence of multimorbidity among females than among males.

The inconsistency in sex-specific risks between the studies may be explained by the different clinical settings, where the initial studies (Studies I, II, and III) relied on national registers primarily capturing specialist and hospital-based care data (Ahrén et al., 2023, 2024, 2025) while Study IV used primary care data (Ahrén et al., 2026). It is possible that the "multimorbidity burden" managed in primary care, which often includes high proportions of depression and anxiety, conditions more prevalent in women, has a different relative impact on VTE risk than the more acute or severe somatic conditions captured in hospital registers (Barnett et al., 2012; Ahrén et al., 2026). This hypothesis is supported by observations of sex-specific multimorbidity patterns in primary care, where clusters containing anxiety and depression were identified as more common in females (Prados-Torres et al., 2012).

The consistency of our results across four studies is likely due to the large-scale Swedish nationwide registers (Ludvigsson et al., 2009, 2016), which provide good statistical power and minimize selection bias.

Differences from previous studies may arise from several factors:

- **Study Populations:** Unlike research restricted to high-risk subgroups, our cohort covered the entire age spectrum, showing that multimorbidity is a risk factor even in younger populations. The consistency of the dose-response relationship in a British South Asian population (Magavern et al., 2023) suggests these findings have broad generalizability across different groups.
- **Study Design:** By using a landmark cohort approach (Dafni, 2011), we moved beyond cross-sectional associations to establish temporality, reducing the risk of reverse causality.

- **Methods and Measurements:** We utilized a modified Barnett "counting method" with 45 NCDs (Barnett et al., 2012). Many previous studies used indices, like the Charlson Comorbidity Index developed by Charlson et al. (1987), primarily designed to predict mortality rather than incident disease. Our method captures "high-burden" but "low-fatality" conditions, such as mental health disorders, which significantly contribute to the overall physiological stress.

Interpretation of findings

The biological plausibility of these findings may be based on the shared pathophysiological pathways common to many chronic conditions (Barnes, 2015; Zöller & Connors, 2024). Both multimorbidity and VTE are age-dependent, with their prevalence and incidence rising in older populations (Ahrén et al., 2024; Heit, 2016; Zöller & Connors, 2024). The annual incidence of VTE escalates from approximately 0.001% in children to 1% in individuals over 70 years of age, a trajectory that resembles the age-related accumulation of chronic diagnoses (Ahrén et al., 2024; Anderson et al., 1991; Barnett et al., 2012; White, 2003). This increase may be linked to age-related physiological changes such as hypercoagulability and vascular endothelial dysfunction, which are central to the initiation of thrombus formation (Colling et al., 2021; White, 2003; Zöller & Connors, 2024). These shifts include a progressive decline in natural anticoagulants and a simultaneous increase in procoagulant factors, such as a significant elevation in plasma levels of Factor VIII, fibrinogen, and D-dimer observed in older populations (Rumley et al., 2006), creating a baseline state of hypercoagulability that is further provoked by additional morbidities (Heit, 2015; Rumley et al., 2006; Zöller & Connors, 2024). The accumulation of multiple chronic diseases may be driven by inflammation, specifically chronic low-grade systemic inflammation known as "inflammaging" (Franceschi et al., 2018; St. Sauver et al., 2022; Zöller & Connors, 2024). High levels of circulating inflammatory cytokines, such as IL-6, have been shown to predict the progression of new chronic diseases over time (Fabbri et al., 2015; St. Sauver et al., 2022). In individuals with elevated baseline IL-6, there is an increase in their multimorbidity burden compared to those with normal levels (Fabbri et al., 2015). This systemic inflammation is also a predictor of future VTE events, as established in large longitudinal cohorts (Olson et al., 2014; Zacho et al., 2010). Large proteomic and metabolomic analyses have identified systemic inflammation as a pathway across different NCDs contributing to a prothrombotic state (Pietzner et al., 2021; Zazzara et al., 2025).

Chronic inflammation acts as a persistent stimulus, where elevated concentrations of CRP and TNF- α correlate with an increased number of chronic conditions (Fabbri et al., 2015; St. Sauver et al., 2022; Zazzara et al., 2025). This systemic

thromboinflammation creates a link between innate immunity and coagulation, as cytokines such as IL-6 directly stimulate the hepatic production of fibrinogen and other acute-phase reactants (Colling et al., 2021; Saghazadeh & Rezaei, 2016). Data indicate that higher levels of high-sensitivity CRP and IL-6 are predictive of future VTE occurrence, thus providing a plausible mechanism for the increased risk observed in multimorbid cohorts (Ding et al., 2023). This has been established in large prospective cohorts that identified increased CRP levels as a significant risk factor for incident VTE events (Olson et al., 2014; Zacho et al., 2010).

The prothrombotic environment in multimorbid individuals is further increased by specific metabolic alterations, such as those observed in diabetes mellitus, where the loss of the endothelial glycocalyx and systemic hypercoagulability contribute to risk (Colling et al., 2021). It has been suggested but not confirmed in other studies that individuals with diabetes face an increased risk of developing VTE compared to nondiabetic controls (Petrauskiene et al., 2005). Diabetes represents a state where acute hyperglycemia can happen with immediate endothelial dysfunction and coagulation activation (Nieuwdorp et al., 2006). In cardiometabolic clusters, heart failure has a chronic maladaptive inflammatory state, maintaining a prothrombotic milieu through elevated concentrations of circulating inflammatory mediators (Chong & Lip, 2007). This prothrombotic state in heart failure is characterized by elevated concentrations of circulating TNF- α and its soluble receptors, which directly activate the vascular endothelium (Chong & Lip, 2007; Levine et al., 1990). Obesity serves as another chronic inflammatory stimulus, where adipocytes secrete cytokines that drive the polarization of anti-inflammatory M2 macrophages toward proinflammatory M1 phenotypes, which in turn impair fibrinolysis and promote thrombus persistence (Colling et al., 2021; Lin & Li, 2021).

A component of this biological link may be the increased bedridden time due to multiple diseases (Cao et al., 2021; Zöller & Connors, 2024). Patients with high multimorbidity severity are more likely to experience periods of immobility, which result in venous stasis (Cao et al., 2021; Zöller & Connors, 2024). This stasis is particularly pronounced in elderly and multimorbid patients, where it has been shown that contrast material can remain longer in the deep veins of older patients for up to an hour after venography (McLachlin et al., 1960).

Evidence suggests that the risk of DVT is substantially higher in patients with prolonged bed rest durations, highlighting the cumulative effect of inactivity in individuals with a high comorbidity index (Cao et al., 2021; Charlson et al., 1987). This stasis constitutes a component of Virchow's triad (Virchow, 1856), reducing the clearance of activated coagulation factors and increasing their local concentration (Wolberg et al., 2012; Zöller & Connors, 2024). Pathological studies have confirmed that such thrombi typically initiate within the venous valve pockets, where flow stagnation is most extreme (Sevitt, 1974).

Prolonged sitting increases circulating inflammatory factor levels and reduces the efficiency of the skeletal muscle pump (Stick et al., 1992), thereby promoting venous thrombosis (Danin-Mankowitz et al., 2021; Healy et al., 2010). The lack of skeletal muscle pump activation during prolonged immobility leads to local hypoxia within venous valve pockets (Budnik & Brill, 2018).

This hypoxia triggers innate immune responses, including mast cell activation and the release of histamine and TNF- α , which further activate the vascular endothelium and promote leukocyte recruitment (Budnik & Brill, 2018; Ponomaryov et al., 2017). Furthermore, activated neutrophils recruited to these stagnant sites may extrude NETs, providing a scaffold for platelet recruitment and initiating the intrinsic coagulation pathway (Ding et al., 2023; von Brühl et al., 2012). NETs are recognized as key mediators in "sterile" VTE, where the systemic inflammatory burden of multimorbidity provides the stimulus for their formation (Budnik & Brill, 2018; Savchenko et al., 2014).

While regular physical activity is generally protective by enhancing fibrinolytic activity (van den Burg et al., 2000) and improving coronary endothelial function (Hambrecht et al., 2000; Kunutsor et al., 2020; Wolberg et al., 2012), the high prevalence of physically inactive behavior in multimorbid populations effectively removes these physiological safeguards (Dhalwani et al., 2017; Kunutsor et al., 2020; Wolberg et al., 2012). Regular exercise improves potential risk factors such as body weight and lipids (Mora et al., 2006) and reduces systemic inflammation, thereby lowering the concentration levels of CRP (Church et al., 2002; Kunutsor et al., 2020). On the other hand, physical inactivity, which is common in disease clusters such as the psychiatric (F2) and cardiometabolic (F1) clusters, contributes to the state of venous stasis driven by the lack of skeletal muscle pump activation (Stick et al., 1992) and chronic inflammation that heightens VTE susceptibility (Ahrén et al., 2024; Borch et al., 2010; Dhalwani et al., 2017; Kunutsor et al., 2020; Olson et al., 2014; Zacho et al., 2010).

The psychiatric cluster (F2), comprising affective disorders, anxiety, and schizophrenia, demonstrated an association with VTE risk (Ahrén et al., 2024). This association may reflect a combination of shared neurobiological vulnerabilities and behavioral factors (Khandaker et al., 2020; Tazzeo et al., 2023; Zöller et al., 2025). A central biological mechanism may be chronic low-grade systemic inflammation, where elevated levels of proinflammatory cytokines, such as IL-6, serve as a common driver for both mental health conditions and a prothrombotic state (Franceschi et al., 2018; St. Sauver et al., 2022). This relationship may be mediated by physical inactivity, which is prevalent in this patient population and leads to venous stasis through impaired skeletal muscle pump function (Stick et al., 1992; Tazzeo et al., 2023).

The underlying genetic structure of these associations involves a complex interplay of shared biological pathways and pleiotropy (Langenberg et al., 2023; Zöller &

Connors, 2024). Evidence from GWAS indicates that approximately 46% of multimorbidity cases are genetically interpretable, suggesting a role for genetic background in disease clustering (Dong et al., 2021). These findings suggest that common genetic variants contribute to the co-occurrence of chronic diseases across the adult population (Dong et al., 2021; Murrin et al., 2025). While nationwide family studies suggest a weak shared familial susceptibility between the total multimorbidity burden and VTE, genetic components have been suggested for specific disease clusters (Ahrén et al., 2023; Zöller et al., 2024).

Pedigree-based approaches have shown that VTE density in families is significantly associated with offspring risk of obesity, diabetes, and arterial embolism, suggesting a shared heritable predisposition for cardiometabolic multimorbidity and thrombosis (Zöller et al., 2024).

Mendelian randomization analyses have further shown these links by identifying causal factors, such as obesity and smoking, that independently increase the risk for both VTE and various multimorbidity phenotypes (Liang et al., 2025; North et al., 2023). MR analyses have also identified specific genomic risk loci, including *CDKN2B-AS1*, *LPA*, and *TCF7L2*, which influence multiple conditions through pleiotropic effects, thereby contributing to the simultaneous development of NCDs and an inherent susceptibility to thrombosis (Murrin et al., 2025; Zhao et al., 2024). Additionally, MR data suggest that educational attainment may causally influence multimorbidity risk, possibly mediated through lifestyle choices such as smoking and physical activity (North et al., 2023).

Methodological Considerations: Strengths and Limitations

Study I

A strength of Study I lies in the use of Swedish national registers, which provide high coverage and validity for the included 2,694,442 unique individuals (Ludvigsson et al., 2011, 2016). The use of a modified and validated list of 45 NCDs, adapted from Barnett et al. (2012), allowed for an assessment of multimorbidity severity. The large sample size provided statistical power to investigate even rare familial associations. A limitation is the cross-sectional study design, which prevents the determination of temporal sequences and causal inferences.

Inclusion was restricted to Swedish-born individuals with Swedish-born parents, which may limit the generalizability of the findings to other populations. The study population was relatively young, making generalizability to older populations uncertain. The potential for reverse causality exists, particularly for conditions such

as atrial fibrillation, which may exhibit bidirectional associations with VTE. The registers lacked data on biological and environmental risk factors such as smoking, BMI, and physical activity. To address this, educational level was used as a proxy for lifestyle factors in the adjusted models (Winkleby et al., 1992). Furthermore, information on temporary provoking factors such as recent travel, pregnancy, or immobilization was unavailable, which could lead to residual confounding.

Study II

A strength of Study II is the application of PCA (Sainani, 2014) to identify nonrandom disease clusters, providing further understanding of how co-occurring NCDs are associated with VTE (Busija et al., 2019). The study benefited from the high diagnostic accuracy of VTE (90%–95%) within the NPR (Andersson et al., 2022; Ludvigsson et al., 2011). The use of ICD-10 codes throughout the study period minimized the risks associated with inaccurate coding. Similar to Study I, the extended cross-sectional design remains a limitation, as it does not allow for establishing temporal associations between the clusters and VTE. Some disease clusters, such as those involving Parkinson's disease or dementia, had few cases, which limited the ability to draw conclusions for those specific groups. Bias was addressed by adjusting for sex, birth year, region of birth, and educational attainment, although the lack of direct lifestyle data remains a constraint. Confounding by individual diseases within the clusters was considered; however, adjusting for specific diseases would have made comparisons among the nine clusters difficult. Educational attainment was again used to compensate for missing sociobehavioral data (Winkleby et al., 1992).

Study III

Study III is strengthened by its prospective cohort design using a landmark approach (Dafni, 2011; Morgan, 2019), which established a temporal association between multimorbidity and incident VTE. The creation of three distinct landmarks with varying follow-up times ensured the robustness of the dose-graded findings and minimized immortal-time bias (Morgan, 2019). The inclusion of death and emigration as competing events in the Fine-Gray models (Fine & Gray, 1999) provided more accurate HRs. A limitation of this proof-of-concept study is the static assessment of multimorbidity at each landmark, which does not account for changes in health status during the follow-up period. The study was limited to Swedish-born individuals to ensure PIN accuracy (Ludvigsson et al., 2009). Confounding was addressed through adjustments for sociodemographic variables, although the lack of information on anticoagulants, antiplatelet therapy, and hormonal treatments remains a limitation. While cancer was included in the multimorbidity definition to account for a major provoking factor, other factors, such as recent hospitalization

for nonmultimorbid conditions, were not fully captured. The parallel log-log survival curves indicated that the proportional hazards assumption was not violated, reducing the risk of model bias.

Study IV

The primary strength of Study IV is the inclusion of primary care data covering approximately 90% of the Swedish population, which significantly enhances the generalizability of the results. Unlike previous studies, this cohort included both Swedish-born and foreign-born individuals, allowing for the discovery of novel interactions between multimorbidity and country of birth. The study also utilized comprehensive adjustments for inherited risk factors, such as FVL and APC deficiency. A methodological limitation was the exclusion of individuals using oral contraceptives or HRT. This may affect the generalizability of the findings to these specific groups. Bias was minimized by excluding prevalent VTE cases and those receiving anticoagulants at baseline to ensure temporal integrity. Confounding was addressed through sensitivity analyses and the use of two landmark timepoints (Morgan, 2019) to validate the impact of diagnostic practice changes. Despite these efforts, the absence of biological data such as blood pressure or BMI remains a limitation common to register-based studies.

Clinical and Public Health Implications

The association between multimorbidity severity and VTE risk suggests that a simple counting method of NCDs may enhance risk stratification (Barnett et al., 2012; Åhrén et al., 2023). The identification of specific disease clusters may allow for a more precise assessment of VTE risk than considering diseases in isolation (Åhrén et al., 2024; Rosendaal, 1999). Clinical practice could therefore move toward incorporating cumulative disease burden into the initial evaluation of patients (Åhrén et al., 2026; National Institute for Health and Care Excellence [NICE], 2016; World Health Organization (WHO), 2016).

The discovery that seven of the nine disease clusters are associated with VTE indicates that preventive efforts may be personalized based on a patient's unique multimorbidity profile (Åhrén et al., 2024, 2025). For instance, the psychiatric cluster (F2) represents a vulnerable population where VTE risk might be overlooked in traditional cardiovascular assessments (Åhrén et al., 2024; Kowal et al., 2020). By recognizing these specific clusters, healthcare providers may initiate earlier clinical surveillance or pharmacological prophylaxis in high-risk patients who do not currently meet standard criteria based on single risk factors (Rosendaal, 1999; Zöller & Connors, 2024).

From a public health perspective, the prevalence of multimorbidity across all age groups underscores the need for broad preventive measures (Ahrén et al., 2023). While multimorbidity is age-dependent, its presence in younger populations suggests that early-life lifestyle factors and social determinants of health, such as educational attainment and neighborhood deprivation, are important drivers of future VTE incidence (Ahrén et al., 2025; Barnett et al., 2012; WHO, 2016). Our findings regarding the higher relative impact of multimorbidity among middle-aged individuals and foreign-born highlight specific target groups for public health interventions aimed at reducing the aggregate disease burden (Ahrén et al., 2026).

Current clinical guidelines for VTE management are largely derived from randomized trials that exclude multimorbid patients, leading to uncertainty in clinical practice (Fortin et al., 2006; NICE, 2016; WHO, 2016). Our results suggest that multimorbidity may be integrated into existing diagnostic and prognostic tools and prediction rules, such as a modified Wells score, to increase diagnostic accuracy in patients with complex needs (Ahrén et al., 2026; Wells et al., 2003). There is a need for future guidelines to adopt a multidisease framework that accounts for the potential interactions among various medications and conditions (Ahrén et al., 2023; Tinetti et al., 2012; WHO, 2016). Clinical practice may evolve to prioritize patient-centered goals and shared decision-making, ensuring that the management of VTE is balanced against the total treatment burden experienced by individuals with multiple chronic conditions (Marcucci et al., 2013; NICE, 2016; WHO, 2016).

Future Research Directions

Future research should prioritize identifying specific biological markers, such as IL-6 or Cystatin C, that may mediate the association between high multimorbidity scores and a prothrombotic state (Pabinger & Ay, 2009; St. Sauver et al., 2022; Zazzara et al., 2025). Given the shared familial susceptibility observed in Study I, further investigation into the genetic determinants and pleiotropic pathways contributing to VTE susceptibility in multimorbid individuals is warranted (Ahrén et al., 2023; Liang et al., 2025; Zöller & Connors, 2024). Establishing causal links between modifiable factors and cardiometabolic multimorbidity could provide essential targets for primary prevention (Li et al., 2025). The optimization of treatment strategies is another future research direction, as multimorbid patients face a higher risks of recurrence and bleeding complications during anticoagulant therapy (Liang et al., 2025; Zöller & Connors, 2024). Such optimization could be achieved through the development of individualized management protocols that utilize shared decision-making and multidisease frameworks to balance thrombotic protection against an increased risk of hemorrhage, while explicitly accounting for the complex interactions among co-occurring conditions and polypharmacy.

Methodologically, while Study III provided proof of concept for incident VTE using a landmark approach, future studies should aim to strengthen the evidence base through large-scale prospective cohort studies and RCTs (Ahrén et al., 2025; Zöller & Connors, 2024). Further studies are needed to evaluate the efficacy and safety of individualized thromboprophylaxis in patients with high multimorbidity scores (Liang et al., 2025; Marcucci et al., 2013). Such trials should ideally implement a multidisease framework to stratify participants based on their cumulative multimorbidity score, evaluating whether individualized thromboprophylaxis protocols can effectively decrease VTE incidence without unacceptably increasing the risk of major bleeding or adverse drug-drug interactions in a population often characterized by significant polypharmacy. Additionally, mechanistic studies are needed to investigate the biological pathways, such as "inflammaging" and metabolic dysregulation, that link chronic disease accumulation to Virchow's triad (Ahrén et al., 2025; St. Sauver et al., 2022; Virchow, 1856; Zöller & Connors, 2024).

Clinical implications may include the development and validation of advanced prediction models for VTE risk (Ahrén et al., 2026). Moreover, the evaluation of prolonged anticoagulant treatment in multimorbid patient groups remains an important area for future research, particularly regarding the balance between thrombotic and hemorrhagic risks (Liang et al., 2025). Finally, as Studies I–IV relied primarily on Swedish registry data, international and population-based research is needed to examine whether these observed associations are consistent across different ethnic populations and diverse healthcare systems (Ahrén et al., 2023, 2025).

Conclusions

This thesis demonstrates that multimorbidity, defined as the co-occurrence of two or more chronic NCDs, is a robust and independent predictor of VTE (Ahrén et al., 2023, 2025). In our nationwide cross-sectional analysis, individuals with multimorbidity exhibited a significantly higher risk of VTE compared to those with 1 or no diseases (Ahrén et al., 2023). This association was further validated in a longitudinal landmark cohort study (Ahrén et al., 2025). Even when diagnosed within a primary care setting, multimorbidity remained an independent risk (Ahrén et al., 2026).

A central finding of this research is the dose-graded relationship between multimorbidity severity and VTE incidence (Ahrén et al., 2023, 2025). Seven of the nine identified multimorbidity clusters showed significant associations with VTE (Ahrén et al., 2024, 2026). From a clinical and epidemiological perspective, these results suggest that multimorbidity scores carry predictive value (Ahrén et al., 2023, 2025). While significant familial associations between clustering of multimorbidity and VTE were found, the primary driver of risk appears to be individual accumulated morbidity (Ahrén et al., 2023). These findings indicate that integrating a multidisease framework into existing risk assessment tools could improve VTE risk stratification and resource allocation in both specialized and primary care (Ahrén et al., 2025, 2026).

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Use of AI tools

Generative AI tool (Google NotebookLM, Google) was used for language editing and improving the clarity of the text. No AI tool was used for data analysis, interpretation of results, or generation of scientific content. All content has been reviewed and approved by the author.

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