

Cohort Profile: *The Danish Venous Thromboembolism Cohort* – A Linkage Between Danish National Health Surveys and Health Registers

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Introduction: Venous thromboembolism (VTE) is a common disease with a serious prognosis. Nonetheless, many aspects of this multicausal disease are poorly understood. The aim of establishing *The Danish Venous Thromboembolism Cohort* was to study VTE risk and prognosis within a life-course context.

Methods: *The Danish Venous Thromboembolism Cohort* was based on respondents to the questionnaire-based Danish National Health Survey (DNHS) conducted in 2010, 2013, and 2017 and was linked to Danish national health and administrative registries.

Results: A total of 474,022 unique respondents to the DNHS were included in this cohort, 8,460 of whom were diagnosed with VTE before the survey response date. The survey's response rate varied between 54% and 60%. The median age at the survey response date was 54 years (interquartile range: 40–66 years), and 46.1% of respondents were men. The cohort contains detailed information on lifestyle factors (smoking habits, alcohol consumption, physical activity level, and dietary habits), health status indicators (healthcare-seeking behavior, body mass index, self-rated health, and mental distress), and self-reported morbidities. In addition, the survey data were linked to records in Danish medical and administrative registries to obtain information on clinical data and outcomes, including hospitalizations, medication use, laboratory test results, labor market participation, vital status, and causes of death.

Discussion: *The Danish Venous Thromboembolism Cohort* is a valuable data resource for use in future studies on VTE research, with a focus on risk factors, complications, interactions, and prognosis.

Keywords: venous thromboembolism, health registries, national surveys, lifestyle factors, cohort

Introduction

Venous thromboembolism (VTE) is characterized by the occurrence of a blood clot in a vein. VTE includes deep venous thrombosis (DVT) and pulmonary embolism (PE). In DVT, a blood clot develops in situ in deep veins, typically in the legs; in PE, a clot fragment from a leg vein breaks off, travels to the lungs, and causes arterial blockage.¹ VTE is a complex, multicausal disorder with an overall incidence rate of one to two events per 1,000 person-years.^{2–7} However, the incidence rate of VTE is notably higher among individuals 55 years or older (10 VTEs per 1,000 person-years).^{8,9}

A wide range of risk factors have been associated with VTE. Well-established risk factors include surgery, cancer, and immobilization, as well as long-term risk factors (eg, genetic and transient acquired factors).^{10–14} Additionally, individuals with a history of VTE, obesity, smoking habits, oral contraceptive use, or a sedentary lifestyle have been reported to have an elevated risk of VTE.^{11–22} Some risk factors originate in early life,²³ highlighting the importance of adopting a life-course perspective when studying VTE risk and prognosis. Despite advancements in understanding these risk

factors in the past decades, 30%–50% of VTE episodes occur without an identifiable provoking factor and are therefore classified as unprovoked.¹⁰

VTE is associated with increased risk of mortality and short- and long-term morbidity, contributing significantly to disability-adjusted life years lost among hospitalized patients.²⁴ In addition, it incurs substantial healthcare costs.²⁵ Survivors of VTE face a poor prognosis, with an average 1-year mortality risk of 10%.^{26,27} Two Danish studies showed that people with VTE remain at an elevated risk of death for up to 30 years after the initial event, with cancer being the primary cause of death, followed by cardiovascular and respiratory diseases.^{26,27}

Therefore, improving understanding of VTE within a life-course context is crucial. Knowledge gaps remain, particularly regarding how major lifestyle factors interact with social determinants, multiple morbidities, treatments, and surgical procedures in relation to VTE.^{28–34}

The Danish Venous Thromboembolism Cohort was established to study VTE within a life-course context. Its goal is to enhance understanding of how health, lifestyle, and social factors interact and influence VTE risk and prognosis in the Danish population. This publication provides information on the cohort's establishment and presents its characteristics, thereby serving as an important reference for researchers using these data.

Materials and Methods

Setting

The Danish Venous Thromboembolism Cohort was based on respondents to the Danish National Health Survey (DNHS).^{35,36} In Denmark, the National Health Service provides universal tax-supported healthcare, ensuring unrestricted access to hospitals and general practitioners, along with partial reimbursement for prescribed medications.³⁷ Unambiguous linkage of all Danish administrative and health registries is possible on an individual level, through the unique personal identification number assigned to Danish citizens upon birth or immigration.^{37,38} This system, combined with administrative, socioeconomic databases, and national surveys, provides a unique platform for studies on lifestyle and social factors.

The Danish National Health Survey

The DNHS (in Danish: *Den Nationale Sundhedsprofil*) is a comprehensive nationwide survey of the general adult population of Denmark (age ≥ 16 years).^{35,36} The survey was based on self-administered questionnaires, and the overall aim was to monitor the status and trends in physical and mental health, health behavior, and morbidity in the Danish population. The DNHS was conducted in 2010, 2013, 2017, and 2021 from the beginning of February to the beginning of May. In each wave, the surveys were based on six mutually exclusive random subsamples: one national sample and five subsamples coming from the five Danish regions (Capital Region of Denmark, Central Denmark Region, North Denmark Region, Region of Southern Denmark, and Region Zealand). The 2021 DNHS data were not yet available at the time of creating the VTE cohort and therefore not initially included in this cohort. They will be included upon request.

Survey Data and Response Rate

The key baseline variables recorded in the DNHS included each participant's personal identification number, self-reported social and lifestyle factors, and health status variables recorded after the completion of either the paper or online questionnaire.^{35,36} The questionnaire was completed by 117,639 participants in 2010, 162,283 participants in 2013, and 183,372 participants in 2017. A valid response was defined as answering a minimum of three questions (age, sex, and any other question). The response rates were 59.5% in 2010, 54.0% in 2013, and 58.7% in 2017. Across all surveys, the response rates were consistently lower among men (55.5% in 2010, 50.4% in 2013, and 54.8% in 2017) than women (63.4% in 2010, 57.5% in 2013, and 62.6% in 2017). Furthermore, the response rates were lower among individuals who had a non-Danish ethnic background, had fewer than 10 years of education, were unemployed or outside the labor market, and were unmarried.^{35,36}

The Danish Venous Thromboembolism Cohort

The Danish Venous Thromboembolism Cohort was established based on all respondents to the 2010, 2013, or 2017 DNHSs. After restricting the survey participants to the first-time respondents, we excluded those younger than 18 years at the time of the survey (Figure 1). Data collection for all surveys was completed in early May in each wave; therefore, May 1st was defined as the baseline date for all survey participants.

We identified all persons from Denmark with a primary or secondary discharge diagnosis of VTE from an in- or outpatient clinic in the Danish National Patient Registry, which covers all Danish hospitals. The diagnoses were determined according to *International Classification of Diseases, Eighth Revision* (ICD-8) codes 450, 451, 452, 453, 671 and 673, and *Tenth Revision* (ICD-10) codes of I26, I80, I81, I82, O88.2, T81.7C and T81.7D. Information on VTE diagnoses (diagnosis code, diagnosis type, date of admission, and discharge date) was associated with the survey respondents to identify people with a pre-survey VTE diagnosis (Figure 1).

Record Linkage to the Danish National Health and Social Registries

Cross-linking of the DNHS data to Danish population-based health and administrative registries ensured essential additional baseline and longitudinal follow-up data for research on VTE (Figure 2). The key national health and administrative registries used in *The Danish Venous Thromboembolism Cohort* are described below.

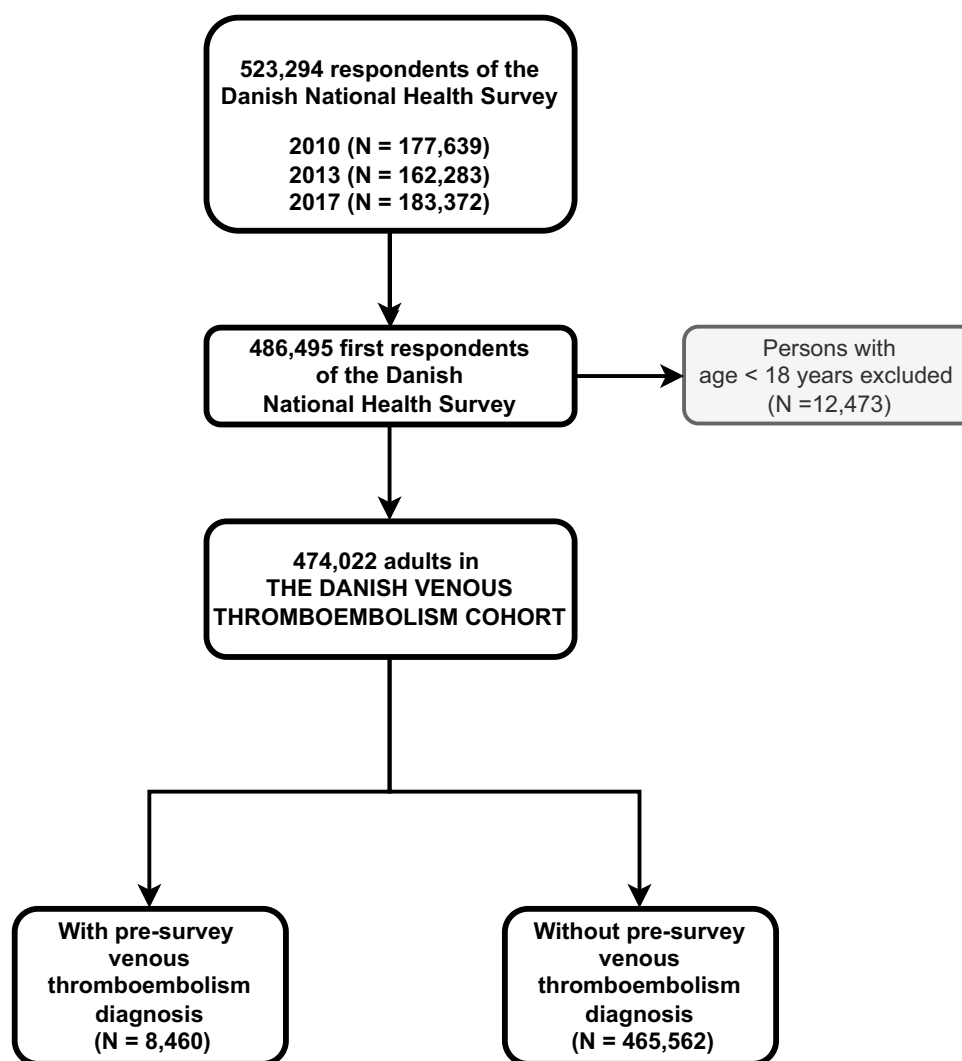


Figure 1 Flowchart of data collection in *The Danish Venous Thromboembolism Cohort* study.

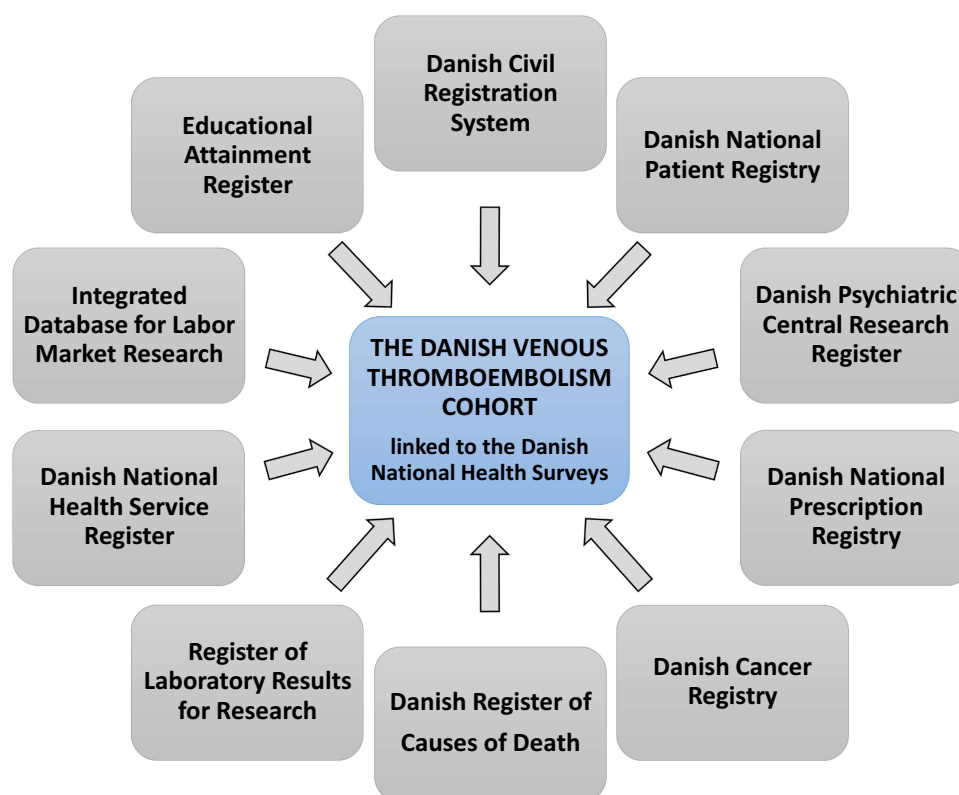


Figure 2 Schematic overview of individual-level data linkage in *The Danish Venous Thromboembolism Cohort*.

- *The Danish Civil Registration System*: Established in 1968, this registry contains individual-level information for all residents in Denmark and provides daily updates on vital statistics, including dates of birth, migration, emigration, and death.³⁸ We linked the survey participants to the Civil Registration System, providing a unique ten-digit identification number to each person, allowing for record linkage at the individual level.
- *The Danish National Patient Registry and The Danish Psychiatric Central Research Register*: The Danish National Patient Registry contains all admissions to Danish non-psychiatric hospitals since 1977 and emergency department and outpatient clinic visits since 1995.³⁹ The discharge diagnoses are classified according to ICD-8 codes through 1993 and ICD-10 codes thereafter. The Danish Psychiatric Central Research Register contains information on every inpatient psychiatric encounter from 1970 onward and became integrated into the Danish National Patient Registry in 1995.⁴⁰
- *The Danish National Prescription Registry*: Data on dispensed medications were extracted by linking the Danish National Prescription Registry to the survey data.⁴¹ This registry contains detailed information on prescriptions redeemed in Denmark since 1995. Medication dispensing can be identified according to the corresponding *Anatomical Therapeutic Chemical (ATC)* codes.
- *The Danish Cancer Registry*: This registry holds information on all incident cases of cancer since 1943 and includes detailed data on tumor characteristics such as topography, morphology, behavior, tumor extent at the time of diagnosis, and date of diagnosis.⁴² These data are essential for research on cancer-related VTE.
- *The Danish Register of Causes of Death*: This registry covers all causes of death among citizens in Denmark since 1970.⁴³ The underlying cause of death, as well as the immediate cause and any contributing causes of death, are recorded with ICD-10 codes.
- *The Register of Laboratory Results for Research*: The Register of Laboratory Results for Research, with complete nationwide coverage since 2015, includes biomarker results (biomarker name, sampling date, *Nomenclature for*

Properties and Units [NPU] code, and test results) collected by general practitioners and hospitals through the electronic hospital laboratory systems.⁴⁴

- *The Danish National Health Service Register*: This registry contains information on the use of health services provided by general practitioners and other medical contractors in primary healthcare (eg, psychologists, psychiatrists, and dentists) since January 1, 1990.⁴⁵
- *Indicators of socioeconomic position*: Finally, we retrieved data on indicators of socioeconomic position (such as annual income, education, and employment status) from the *Integrated Database for Labor Market Research*⁴⁶ and the *Educational Attainment Register*.⁴⁷

The extracted data are stored on Statistics Denmark's secure server and have been pseudonymized.

Results

A total of 523,294 respondents to the DNHS conducted in 2010, 2013, and 2017 were identified. After restricting to first-time respondents and those 18 years or older at the time of the survey, *The Danish Venous Thromboembolism Cohort* included 474,022 individuals. In total, 8,460 people were diagnosed with VTE before the baseline date (Figure 1). The median follow-up time, calculated as the time from baseline date to death, emigration, or December 31, 2021 (whichever occurred first), was 7.7 years (interquartile range: 3.7–10.7 years).

Self-Reported Survey Data in The Danish Venous Thromboembolism Cohort

The survey questionnaire content available in *The Danish Venous Thromboembolism Cohort* is presented and described in Table 1. The cohort contains detailed information on age, sex, marital status, and highest completed education level. Lifestyle factors, such as smoking habits (smoking status and cigarettes smoked per day for current smokers), alcohol consumption (days of alcohol intake per week and total number of standard drinks in a typical week), physical activity level, and dietary habits are also available in the cohort. In addition, health status indicators (healthcare-seeking behavior, body mass index [BMI], self-rated health, and mental distress) and self-reported morbidities were retrieved from the DNHS.

Table 1 Survey Questionnaire Content Available in *The Danish Venous Thromboembolism Cohort* and Proportion of Missing Data

Variables	Variable Description, Categories
SOCIODEMOGRAPHICS	
Age	• Age at survey response • Continuous
Sex	• Binary: male, female
Year of survey	• 2010, 2013, 2017
Marital status	• Categorical: never married, widowed, divorced, separated, married, living together; not available (1.5%)
Highest completed education	• Categorical: under education, secondary compulsory, vocational/high school, higher education (any university degree or beyond), other education; not available (7.2%)
LIFESTYLE FACTORS	
Smoking habits	• Categorical: never smoked, former smoker, current smoker; not available (3.1%) • Continuous: average number of cigarettes per day; not available (5.2%)
Alcohol consumption	• Categorical: days of alcohol intake per week: 1–2, 3–4, 5–6, or 7 days/week; not available (14.5%) • Continuous: total number of standard drinks in a typical week (a standard drink contains 12 grams of pure alcohol); not available (6.0%)

(Continued)

Table 1 (Continued).

Variables	Variable Description, Categories
Physical activity	• Binary: no, yes; not available (35.5%) • Continuous: intensity of physical activity (number of hours/minutes with moderate or hard physical activity)
Dietary habits	• Categorical, defined as self-rated dietary habits: healthy, reasonably healthy, unhealthy; not available (6.1%)
HEALTH STATUS VARIABLES	
Healthcare-seeking behavior	• Defined as a visit to a general practitioner within 12 months • Binary: no, yes; not available (3.7%)
Self-rated health	• Using the 12-item short-form health survey SF-12v2 • Categorical: excellent, very good, good, fair, poor; not available (1.1%) • Continuous: physical health and mental health t-scores; not available (4.6%)
Body mass index (BMI)	• Continuous: in kg/m² • Categorical: <18.5, 18.5–24.9, 25–29.9, or 30+ kg/m²; not available (4.6%)
Anxiety, nervousness, or unrest	• Defined as experiencing symptoms within the prior 14 days • Categorical: no; yes, bothered a lot; yes, bothered only a little; not available (3.2%)
Sleeping difficulty	• Defined as experiencing symptoms within the prior 14 days • Categorical: no; yes, bothered a lot; yes, bothered only a little; not available (3.1%)
SELF-REPORTED MORBIDITIES	
Cancer	• Binary: no, yes; not available (7.3%)
Diabetes	• Binary: no, yes; not available (7.6%)
Chronic obstructive pulmonary disease	• Binary: no, yes; not available (7.0%)
Hypertension	• Binary: no, yes; not available (6.2%)
Osteoporosis	• Binary: no, yes; not available (7.2%)
Rheumatoid arthritis	• Binary: no, yes; not available (8.1%)
Osteoarthritis	• Binary: no, yes; not available (6.5%)

Characteristics of The Danish Venous Thromboembolism Cohort

The Danish Venous Thromboembolism Cohort and the subcohort of people with pre-survey VTE diagnosis were described according to selected baseline sociodemographic characteristics, lifestyle factors, health status indicators, pre-survey morbidities, and medication use, presented as numbers with percentages and medians with interquartile range (Table 2). In addition to individual morbidities, the Charlson Comorbidity Index was used to assess multimorbidity. This index comprises 19 comorbid conditions, each assigned a weight ranging from one to six.⁴⁸

The median age at the baseline date was 54 years (interquartile range: 40–66 years), and 46.1% of respondents were men. A total of 50.0% of respondents reported having a low educational level (ie, under education or secondary compulsory). At the time of the survey, 20.9% of respondents reported being active smokers, and the median BMI was 25.1 kg/m².

Regarding morbidities defined from the National Patient Registry, 7.6% of cohort members had a cancer diagnosis before the baseline date, 5.8% had chronic obstructive pulmonary disease (COPD), and 3.8% had diabetes. Using the individual chronic diseases included in the Charlson Comorbidity Index score (information obtained from the Danish

Table 2 Selected Characteristics of the Survey Participants in *The Danish Venous Thromboembolism Cohort* and Among Cohort Members with a Pre-Survey Venous Thromboembolism Diagnosis

	The Danish Venous Thromboembolism Cohort (N = 474,022)		People with Pre-Survey VTE Diagnosis (N = 8,460)	
	N	%	N	%
SOCIODEMOGRAPHICS				
Age in years, median (interquartile range)*	53.6 (39.7–66.3)		66.8 (55.9–75.7)	
Male sex*	218,480	46.1	4,010	47.4
Year of survey				
2010	173,116	36.5	2,633	31.1
2013	143,438	30.3	2,590	30.6
2017	157,468	33.2	3,237	38.3
Highest completed education**				
Under education	26,163	5.5	85	1.0
Secondary compulsory	210,837	44.5	4,279	50.6
Vocational/high school	133,938	28.3	2,068	24.4
Higher education	48,013	10.1	595	7.0
Other education	21,128	4.5	473	5.6
Missing	33,943	7.2	960	11.3
LIFESTYLE FACTORS**				
Active smoking	99,141	20.9	1,589	18.8
Missing	14,878	3.1	371	4.4
Body mass index, kg/m², Median (interquartile range)	25.1 (22.6–28.1)		26.9 (24.0–30.4)	
Missing	21,581	4.6	471	5.6
MORBIDITIES#				
Charlson Comorbidity Index score				
Comorbidity: 0	360,373	76.0	3,967	46.9
Comorbidity: 1	53,985	11.4	1,562	18.5
Comorbidity: 2	36,201	7.6	1,344	15.9
Comorbidity: 3+	23,463	4.9	1,587	18.8
Cancer	35,896	7.6	1,598	18.9
Myocardial infarction	10,948	2.3	524	6.2
Stroke	12,043	2.5	592	7.0
Heart failure	7633	1.6	573	6.8
Diabetes	18,234	3.8	809	9.6
Chronic obstructive pulmonary disease	27,727	5.8	1,154	13.6

(Continued)

Table 2 (Continued).

	The Danish Venous Thromboembolism Cohort (N = 474,022)		People with Pre-Survey VTE Diagnosis (N = 8,460)	
	N	%	N	%
MEDICATION USE[%]				
Vitamin K antagonists	17,406	3.7	5,202	61.5
Direct oral anticoagulants	6167	1.3	880	10.4
Low-molecular-weight heparin	2646	0.6	901	10.7
Statins	92,128	19.4	3,175	37.5

Notes: *Defined from the Danish Civil Registration System **Variables defined according to self-reported data extracted from the Danish National Health Survey [#] Defined from the Danish National Patient Registry as discharge diagnosis before the baseline date [%]Defined from the Danish National Prescription Registry as redemption of at least one prescription within 1 year before or on the baseline date.

Abbreviation: VTE, venous thromboembolism.

National Patient Registry), 12.5% of the overall cohort had a moderate or severe comorbidity burden with Charlson Comorbidity Index score ≥ 2 (Table 2).

Among people with pre-survey VTE, the median age was 67 years (interquartile range: 56–76 years), and 47.4% were men. At the time of the survey, 51.6% had a low educational level, and 18.8% reported being active smokers. Concerning morbidities identified in the National Patient Registry, the distribution substantially varied by pre-survey VTE diagnosis. Among individuals with pre-survey VTE, 18.9% had a cancer diagnosis, 13.6% had COPD, and diabetes was recorded for 9.6% of the patients.

Information on the use of selected VTE-associated medications within 1 year before or on the baseline date (defined from the National Prescription Registry) are presented in Table 2. VTE-associated treatments, including vitamin K antagonists (61.5% vs 3.7%), direct oral anticoagulants (10.4% vs 1.3%), low-molecular-weight heparin (10.7% vs 0.6%), and statins (37.5% vs 19.4%, respectively), were more frequently used in the pre-survey VTE subcohort than the overall cohort (Table 2).

Discussion

Data on lifestyle factors, such as smoking, alcohol consumption, diet, physical exercise, or health conditions diagnosed only in the primary care setting, are usually not captured in the national administrative and health registries. Consequently, many studies cannot evaluate these factors as exposures, outcomes, or covariates^{10,13,21,26–30} and may suffer from unmeasured or residual confounding. While many studies have collected data on lifestyle factors through self-administered questionnaires, these studies have often included only a limited number of participants or potential recall bias.^{31–33} Data from health surveys provide a unique opportunity to generate a diverse and detailed picture of a population's lifestyle health status; monitor health changes over time; and collect information on lifestyle, social factors, and self-reported health conditions. Such data can contribute to understanding the multicausal nature of VTE, including interactions between genetic, environmental, and lifestyle factors.

The Danish Venous Thromboembolism Cohort is a nationwide, survey-based study from Denmark with longitudinal registry data and long-term follow-up. Multiple sources of healthcare and administrative registries were linked with survey data to provide a comprehensive data platform containing detailed information on demographics, lifestyle factors, socioeconomic variables, treatments, and morbidity patterns. *The Danish Venous Thromboembolism Cohort* provides a foundation for gaining new insights into the clinical epidemiology of VTE in a life-course context.

Strengths and Limitations

This study has several strengths and limitations. The data from the surveys constitute a unique research resource including information on eg, lifestyle factors and self-reported health that are not available in other registries. In this regard, the major strengths of *The Danish Venous Thromboembolism Cohort* include the large number of participants,

with virtually no loss to long-term follow-up; the general population setting; and the diversity of questionnaire content.

A limitation of survey studies is that non-response and missing data can reduce precision, affect generalizability, and introduce bias, thereby leading to under- or overestimation of absolute, but not relative, risk estimates. In the DNHS, the response rate declined between 2010 and 2013 but increased again in 2017. A low response rate may impact the representativeness of the cohort by introducing selection bias of studies in absolute risk, thereby limiting the transportability of the study findings. Calibrated weights were previously calculated and are available for implementation to reduce biases due to differential non-response.^{35,36,49} Methods for handling missing data, such as multiple imputation, weighting, or sensitivity analysis, can help decrease biases when data are missing at random. Multiple measurements from more than one survey are available only for a small proportion (6.9%) of *The Danish Venous Thromboembolism Cohort* members.

The clinical diagnosis of VTE may be difficult. The accuracy of the diagnostic coding of VTE is important for the interpretation of the findings. The VTE diagnosis coding in the Danish National Patient Registry has been validated, with confirmation rates of 88%–90%.^{48,50} The positive predictive values (PPVs) of VTE diagnosis codes decrease from 88% for incident VTE to 72% for recurrent events. However, the PPV increases when combined with a coded ultrasound diagnostic examination.⁵⁰ Among patients with a cancer diagnosis, the overall PPV of an ICD-10 VTE code was 75.9%, while the PPV for recurrent VTE dropped to 44.2%.⁵¹ A similar level of validity applies to data on morbidities extracted from Danish registries.^{39,48,50} Dispensed medication data recorded in the Danish Prescription Registry are highly valid;⁴¹ however, this registry does not include information on medication adherence and does not capture data on over-the-counter medications.

Finally, because the surveys are based solely on questionnaires, they can provide data only on the prevalence of self-reported health conditions. A previous study from Denmark comparing diagnoses reported in the DNHS with registry data has indicated generally high specificity and negative predictive values.⁵² However, substantial variations in sensitivity and PPVs were detected.

Conclusions

The Danish Venous Thromboembolism Cohort was developed to provide a valuable resource for use in future studies on VTE research in a life-course context, with a focus on risk factors, complications, interactions, and prognosis. By combining national survey data with high-quality registry data, the cohort can enhance understanding of VTE risk factors and disease trajectories, thereby supporting the identification of high-risk populations and informing prevention strategies.

Data Sharing Statement

No additional data will be made available, because of data security issues.

Ethics

According to Danish legislation, informed consent and approval from an ethics committee are not required for registry-based studies. Data handling procedures complied with Statistics Denmark's data confidentiality policy. The study was reported to the Danish Data Protection Agency (Aarhus University record no. 2016-051-000001/2249).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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