Cardiovascular disease and heart failure in Greenland: A focus on dilated cardiomyopathy variants among Greenlanders with non-ischemic heart failure

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Acknowledgements and Positioning

I want the thank those who have supported and influenced this work. My family, especially my girlfriend and our daughters, have been my primary drivetrain throughout this journey. I also thank my colleagues at Pikialaarfik and Queen Ingrid's Hospital, whose support has been essential in doing the research. Appreciation goes to my supervisors for their guidance, and to Steno Diabetes Center Greenland and the Karen Elise Jensen Foundation for funding this project. Additionally, I acknowledge Steno Diabetes Center Aarhus for the exchange experience and the Medical Department at Queen Ingrids Hospital for the relentless support.

My journey in Greenland began as a medical doctor at Queen Ingrid's Hospital in Nuuk. Confronted with the challenges of cardiovascular disease and heart failure in the patients, I experienced the health issues in this region. This experience, combined with the opportunity to conduct research in Greenland, led to the start of this project. With a focus on ethical considerations, especially when conducting research in a society like Greenland's, I aimed to enhance understanding of CVD in the region. This study seeks to illuminate cardiovascular disease, hopefully aiding in the improvement of cardiovascular health in Greenland.

Abbreviations

CVD: Cardiovascular Disease

HF: Heart Failure

DCM: Dilated Cardiomyopathy

IHD: Ischemic Heart Disease

EMR: Electronic Medical Records

LVEF: Left Ventricular Ejection Fraction

BMI: Body Mass Index

ICPC-2: International Classification of Primary Care, Second Edition

ICD-2: International Classification of Diseases, Second Edition

WGS: Whole Genome Sequencing

VUS: Variants of Unknown Significance

dbSNP: Database of Single Nucleotide Polymorphisms

ECG: Electrocardiogram

HFrEF: Heart Failure with reduced Ejection Fraction

HFpEF: Heart Failure with preserved Ejection Fraction

HFmrEF: Heart Failure with mildly-range Ejection Fraction

Summary

This thesis investigates the complex landscape of cardiovascular diseases (CVD) in Greenland, with focused attention on heart failure (HF) and the genetics of dilated cardiomyopathy (DCM). It encompasses three relevant studies, each addressing an aspect of cardiovascular health in the indigenous Greenlandic population, characterized by distinct genetic and lifestyle factors.

Study I analyze the incidence and mortality rates of CVD in Greenland from 1994 to 2021. Utilizing nationwide health registers, uncovers a rising trend in CVD, particularly among the elderly. This study highlights the impending challenges for Greenland's healthcare system, emphasizing the need for targeted prevention and management strategies.

Study II shifts focus to HF, exploring its prevalence and clinical characteristics in Greenland. This study reveals a high prevalence of obesity and smoking in the HF cohort, diverging from the patterns observed in other populations. Contrary it discovers a smaller than expected portion of IHD in the cohort.

Study III investigates the genetics involved with DCM in Greenlanders with HF and without ischemic heart disease. Despite a low prevalence of known DCM variants, the study underscores the necessity for broader genetic research in this rather unique genetic population compared to those on which the existing evidence is relying on.

Across all studies, the thesis consistently points to the need for a comprehensive, multidisciplinary approach to prevent CVD. This includes educational initiatives, societal changes, and policy interventions. The thesis suggests promoting healthier lifestyles in schools, implementing policies like taxation on unhealthy foods and cigarettes, and developing infrastructure to encourage physical activities.

In conclusion, this thesis significantly enhances our understanding of CVD, HF, and DCM in Greenland. It underlines the need for nuanced public health strategies and genetic research tailored to Greenland's population. The insights gained contribute to the global narrative on heart health, prevention, and management, highlighting the importance of continuous evolution in genetic and epidemiological research methods to address health challenges in unique populations globally.

Dansk resumé

Denne afhandling udforsker det komplekse landskab af hjerte-kar-sygdomme i Grønland, med særlig vægt på hjertesvigt og genetikken bag. Den omfatter tre relevante studier, der hver især adresserer et unikt aspekt af hjerte-kar-sundhed i den grønlandske befolkning, kendetegnet ved specifikke genetiske og livsstilsfaktorer.

Det første studie analyserer forekomsten og dødeligheden af hjerte-kar-sygdomme i Grønland fra 1994 til 2021. Ved at anvende landsdækkende sundhedsregistre afdækker det en stigende tendens i disse sygdomme, især blandt ældre. Dette studie fremhæver de forestående udfordringer for Grønlands sundhedssystem og understreger behovet for målrettede forebyggelses- og behandlingsstrategier.

Det andet studie fokuserer på hjertesvigt, og undersøger dets udbredelse og kliniske karakteristika i Grønland. Dette studie afslører en høj forekomst af fedme og rygning blandt personer med hjertesvigt, sammenlignet med andre hjertesvigtspopulationer. Modsat findes der en lav forekomst af iskæmisk hjertesygdom.

Det tredje studie undersøger det genetiske område involveret med dilateret kardiomyopati hos grønlændere uden iskæmisk hjertesygdom. På trods af fund af en lav forekomst af kendte varianter af denne sygdom, understreger studiet nødvendigheden af mere omfattende genetisk forskning i denne enestående genetiske population som adskiller sig fra den europæiske hvor den eksisterende evidens er etableret.

På tværs af alle studier peger afhandlingen konsekvent på behovet for en omfattende, tværfaglig tilgang til forebyggelse af hjerte-kar-sygdomme. Dette inkluderer uddannelsesinitiativer, samfundsmæssige ændringer og politiske indgreb. Afhandlingen foreslår at fremme sundere livsstil i skoler, implementere politikker som afgifter på usund mad og cigaretter, og udvikle infrastruktur til at fremme fysisk aktivitet.

Afslutningsvis forbedrer denne afhandling vores forståelse af hjerte-kar-sygdomme, hjertesvigt og dilateret kardiomyopati i Grønland. Den understreger behovet for nuancerede folkesundhedsstrategier og genetisk forskning tilpasset Grønlands unikke befolkning. De opnåede indsigter bidrager til den globale fortælling om hjertesundhed, forebyggelse og behandling, og fremhæver vigtigheden af kontinuerlig udvikling i genetiske og epidemiologiske forskningsmetoder for at tackle sundhedsudfordringer i befolkninger globalt.

Introduction

Cardiovascular disease (CVD) has become the leading cause of mortality globally, with stroke and ischemic heart disease (IHD) contributing to 85% of CVD deaths. This rise in CVD coincides with a decrease in infectious diseases due to medical advancements in the 20th century. Modern treatment approaches and risk factor reduction have significantly decreased CVD mortality, yet recent trends show stagnation in this decline, linked to increasing metabolic disorders like obesity and diabetes.

CVD encompasses various heart and blood vessel conditions, with IHD and stroke being the most prevalent. These conditions share pathogenic pathways and risk factors, including lifestyle choices (smoking, poor diet, sedentary lifestyle) and clinical factors (hypertension, dyslipidemia, diabetes, obesity). Genetics also plays a crucial role in CVD risk, with both monogenic and polygenic factors contributing. The global distribution of CVD is uneven and influenced by lifestyle, environmental factors, healthcare access, and genetic predisposition.

Indigenous populations, such as the Greenlandic Inuit, face a high burden of CVD. In Greenland, the transformation in lifestyle due to globalization has led to increased health issues like obesity, diabetes, and hypertension, raising concerns about the Inuit population's vulnerability to non-traditional diseases, including CVD. Cardiovascular risk factors in Greenland have evolved, with smoking rates remaining high compared to other regions. Clinical factors like hypertension and obesity have seen marked increases. Additionally, genetic studies have identified specific variants in the Greenlandic Inuit associated with increased diabetes and CVD risk.

The history of CVD in Greenland, particularly atherosclerosis, has seen evolving perceptions. Initial observations suggested low incidence rates of myocardial infarction, attributed to high intake of marine fats. However, later studies indicated that CVD prevalence among the Inuit is similar to other populations, with a high stroke mortality rate. Understanding the incidence and prevalence of CVD in Greenland is vital for guiding healthcare strategies and resource allocation. The Greenlandic healthcare system, publicly funded and regionally structured, faces challenges due to geographical constraints and population distribution, impacting the management and outcome of CVD cases.

In summary, the background of CVD in Greenland highlights the need for tailored healthcare strategies that consider the unique genetic composition, lifestyle, and environmental factors of the Inuit population. Continuous research and targeted interventions are crucial in addressing the health and economic implications of CVD in this region.

Thesis papers

Paper I: **Prevalence and clinical features of heart failure in Greenland**
Hjalte Erichsen Larsen, Uka Wilhjelm Geisler, Finn Gustafsson, Marit Eika Jørgensen & Michael Lynge Pedersen, International Journal of Circumpolar Health, 82:1, 2178068, DOI: 10.1080/22423982.2023.2178068

Paper II: **Trends in cardiovascular disease among Inuit in Greenland from 1994 to 2021**
Hjalte Erichsen Larsen, Uka Wilhjelm Geisler, Finn Gustafsson, Michael Lynge Pedersen & Marit Eika Jørgensen,

Submitted, Atherosclerosis Plus.

Paper III: **Genetic screening of Dilated Cardiomyopathy variants among Greenlanders**
Hjalte Erichsen Larsen, Anne Cathrine Baun Thuesen, Marie Balslev Backe, Finn Gustafsson, Torben Hansen, Michael Lynge Pedersen & Marit Eika Jørgensen.

In preparation

Aims

Considering the varied historical understanding of cardiovascular diseases (CVD) in Greenland, our objective was to expand the knowledge base regarding these diseases in this region. Recognizing the distinct genetic makeup of the Greenlandic Inuit population, our research primarily focused on exploring genes associated with Dilated Cardiomyopathy (DCM) in Greenlanders. Our study was structured around three main goals:

I. To determine the incidence and mortality rates associated with diagnosed cases of CVD in Greenland.
II. To assess the prevalence and characteristics of Heart Failure (HF) within the Greenlandic population.
III. To investigate the genetic factors contributing to non-ischemic HF in Greenlanders, specifically by screening for known variants linked to DCM.

Background

Cardiovascular disease

Historically, as the 20th century commenced, infectious disease dominated the global health landscape, significantly reducing life expectancy. However, the medical revolution, characterized by advancements in antibiotics, immunization, and sanitation, led to a marked decrease in communicable diseases, primarily in developed regions. This shift precipitated a rise in life expectancy and, consequently, a rise in non-communicable diseases, particularly cardiovascular disease (CVD) and cancer. Presently, CVD stands as the leading cause of mortality worldwide, responsible for approximately 17.9 million deaths annually, equal to about a third of all global deaths (1). Stroke and ischemic heart disease (IHD) are notably the prime contributors, constituting 85% of all CVD-induced mortality (1). The latter half of the 20th century witnessed a significant decrease in CVD mortality, largely due to the integration of modern evidence-based therapeutic approaches and risk factor reduction (2,3). However, recent data indicates a stagnation in the declining trend, potentially driven by a rising prevalence of metabolic disorders such as obesity and diabetes (3).

CVD includes a range of conditions affecting the heart or blood vessels. These diseases share some pathogenic pathways and risk factors but manifest in a variety of symptoms and require different management (4–6). IHD and stroke are the most prevalent diagnoses, both sharing a similar etiology: they are caused by compromised blood flow to the heart or brain, respectively. CVD also includes conditions such as heart failure (HF), arrhythmias, valvular heart disease, and peripheral arterial disease, among others. Lifestyle factors including smoking, alcohol consumption, poor diet, and sedentary lifestyle are all contributing to CVD risk (7). Research suggests that lifestyle modifications can reduce IHD incidence by up to 80% (7–9). Clinical risk factors like hypertension, dyslipidemia, diabetes, and obesity are linked to CVD (6,7,10). Additionally, psychosocial factors, including affective disorders, chronic stress, and major life challenges, have been correlated with IHD (10).

Genetics also plays a crucial role in the risk of CVD, with a family history of CVD being a well-established independent predictor for CVD events (11). Both monogenic (single gene) and polygenic (multiple genes) factors contribute to CVD risk. Monogenic variants, although rare, can confer large disease risks. For instance, familial hypercholesterolemia is caused by mutations in the *LDLR* gene, responsible for encoding the low-density lipoprotein receptor (12). In contrast, polygenic risk involves common genetic variations, each having a small individual effect, but collectively they contribute significantly to disease risk (12). As genetic profiling becomes more widespread, the evidence of polygenic risk for CVD is increasing.

Consequently, the assessment of CVD risk may soon incorporate a polygenic risk score equivalent to the clinical factors used today (13).

The factors contributing to the risk of developing CVD are numerous, leading to an uneven global distribution of CVD across populations. The disparity arises from a combination of components, including lifestyle, environmental influences, health care accessibility and quality, ethnicity, and genetic predisposition (14–17). Over the past 25 years, regions with a very high sociodemographic index have seen the largest declines in CVD mortality, while most regions have only witnessed gradual decreases or no change in CVD rates (18).

Indigenous people worldwide face unique health challenges, with a disproportionately higher burden of CVD (19). These challenges are often attributable to socio-economic factors, environmental changes, and lifestyle transitions. Indigenous populations are frequently marginalized, facing limited access to healthcare, economic opportunities, and experiencing the repercussions of rapid cultural changes (20). High prevalence of CVD risk factors like obesity, diabetes, smoking, and hypertension combined with possible genetic factors contribute to a rise in non-communicable diseases, including CVD (20).

The diversity in CVD across different populations underscores the need for region-specific research and tailored healthcare approaches. Understanding the cardiovascular health profiles, shaped by genetics, lifestyle, and environmental factors, is crucial in developing effective prevention and treatment strategies. This approach is particularly vital in places like Greenland, where the indigenous population's distinct lifestyle and genetic makeup, coupled with unique environmental stressors, may lead to atypical cardiovascular health patterns. Continuous research in these areas not only addresses the global health inequity challenge but also bears significant economic implications. CVD costs billions annually in healthcare expenses and productivity losses globally, making targeted interventions and novel diagnostics crucial for both health and economic reasons (21).

Heart failure

Heart failure (HF) is a clinical syndrome marked by symptoms like breathlessness, fatigue, and fluid overload, leading to compromised heart function (22). HF significantly impacts mortality rates, quality of life, and is a leading cause of hospitalization (22,23). Mortality from HF mirrors that of common cancers, with survival rates decreasing dramatically over time (24–27). The prevalence of HF in developed countries is about 1-2% in adults, increasing with age, and it's estimated that around 5% of individuals over 75 and 10% over 85 are affected (28–32). Factors such as age, hypertension, ischemic heart disease, diabetes, and obesity significantly contribute to HF risk (33–35).

HF is categorized based on the left ventricular ejection fraction (LVEF), with three classifications: heart failure with reduced ejection fraction (HFrEF, LVEF < 40%), mildly reduced ejection fraction (HFmrEF, LVEF 41-49%), and preserved ejection fraction (HFpEF, LVEF > 50%). Diagnosing and treating HFpEF remains challenging, with limited options compared to HFrEF (36). Treatment for HFrEF has evolved significantly, including pharmacological and device-based interventions to improve heart function (22).

Dilated cardiomyopathy

Cardiomyopathies represent a diverse group of diseases and are a common cause of HF (22). Dilated cardiomyopathy (DCM) stands out as the most prevalent form (22). It is characterized by the dilation and impaired function of the left ventricle, or both ventricles, without IHD or abnormal loading conditions as contributing factors (37). The etiology of DCM includes genetics along with myocardial damaging conditions like infectious or toxic agents, endocrine and metabolic disturbances, immune-mediated mechanisms, and peripartum cardiomyopathy (38).

Advancements in genetic research have significantly deepened the understanding of DCM, particularly with modern genome sequencing technologies. These advancements have shed light on the genetics involved with DCM, revealing it to have both monogenic and polygenic components (37). However, to conclusively identify disease-associated genes, it is necessary to understand the genetic background of the affected population and conduct comprehensive genetic research (39).

The Greenlandic Inuit

The narrative of the Greenlandic Inuit is a testament to human resilience and adaptability. The contemporary Greenlandic Inuit are descendants of the Inuit of the Thule culture, which is believed to have established roots in northern Greenland around 1200 BC (40,41). These initial settlers are thought to have migrated from Africa, through Asia, Siberia, and North America during the past 60.000 years (42). As each successive population movement only contained a subset of genetic variation from the previous population, the result was a gradual reduction in genetic diversity the further a population came from Africa (figure 1) (42). Furthermore, genetic drift, a random non-selective phenomenon influencing the allele frequency in a population, has a more pronounced effect on smaller populations. Genetic drift can eventually lead to either fixation, wherein everyone in the population becomes a carrier of a specific allele, or conversely, it can result in the complete depletion of a particular allele in a population (43,44). Research on the genetics of the Greenlandic Inuit has revealed that their status as a bottleneck population for 20,000 years has caused shifts in allele frequencies which is likely attributed to the extreme genetic drift they have experienced (44). Affecting the genetic variation of the Greenlandic Inuit, resulting in a depletion of rare variants and an increase in the frequency of the remaining variants (44).

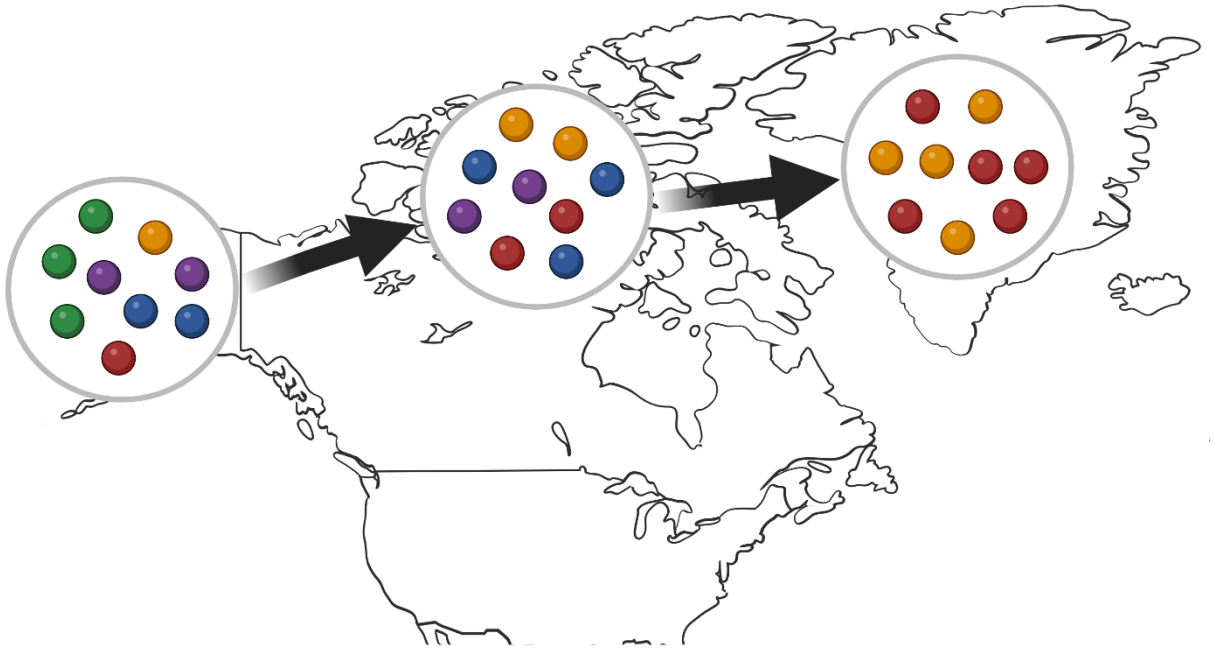

Figure 1. Illustration of the diversity in the human genetic composition as populations migrated into Greenland. Each color within the circles represents different genetic traits, showing a decrease in diversity with each migration.

Through thousands of years, the ancestors of the Greenlandic Inuit migrated on, eventually reaching and settling in what is now known as Greenland, extending their presence from the northern tip down to the eastern and western coastlines (40). In this harsh arctic environment, generations of Inuit lived under extreme climatic conditions, relying on a diet rich in protein and fatty acids derived primarily from sea mammals. Survival depended on an intimate understanding of their environment, mastery of hunting techniques, and the strength of the tightly-knit community. Research indicates that the Inuit have undergone genetic adaptations to these unique living conditions (45). The genetic profile of the Arctic Inuit is distinct from other global populations (40,41). This is attributed to their historical isolation, descent from a relatively small initial population, and the strong positive selection pressures caused by the environment. These genetic traits, which have evolved over thousands of years, played a crucial role in optimizing their metabolism, allowing for adaptation to cold environments, and enabling efficient utilization of energy derived from their traditional diets (45).

Through the past century, the lifestyle of the Greenlandic Inuit has undergone significant transformation due to globalization. Transitioning from an active lifestyle of hunting, fishing, and foraging to a more sedentary existence, coupled with dietary changes from traditional, nutrient-rich foods to processed carbohydrate-heavy diets. This shift in lifestyle has been linked to an increased prevalence of modern health issues such as obesity, diabetes, and hypertension (46,47). The changes are particularly concerning given the genetic composition of the Inuit, which may not be well-suited to cope with the health challenges posed

by a Western diet and lifestyle. This rapid transition raises questions about the increased vulnerability of the Inuit population to non-traditional diseases, including CVD. An understanding of the genetics, lifestyle, and environmental factors is necessary. Knowledge of how these interact can provide insights into the current prevalence and nature of CVD among the Greenlandic Inuit. It underscores the need for tailored health strategies that consider the unique genetic composition and lifestyle of the Inuit population. Such an approach is needed to address and manage CVD in the Greenlandic population, ensuring that interventions and healthcare policies are scientifically sound.

Cardiovascular risk factors in Greenland:

The life expectancy in Greenland has increased markedly over the past decades, reflecting a general improvement in the health status in the country, and can be credited to a decline in maternal and infant mortality as well as deaths due to infectious diseases, especially tuberculosis (48). However, other health challenges are rising or remain prevalent in the population. Since 1993, five nationwide population surveys have been carried out in Greenland. The surveys aim to assess the public health status in Greenland using indicators for both physical and mental health (46). These surveys have presented notable trends in health behaviors and risk factors for CVD. For instance, the prevalence of smoking has declined, from 68% in 1993 to 52% in 2018 (46). Similarly, alcohol consumption has been reduced from 22.2 liters of 100% alcohol per person in 1987 to 7.4 liters in 2018 (49). Dietary patterns have also undergone significant changes. Surveys from 2005-2010 onwards indicate an increased daily consumption of vegetables, from 23.9% to 29.6% in 2018. However, there has been a worrying rise in daily soft drink consumption, from 24.4% to 43.9%, and a decrease in weekly fish consumption, from 56.0% to 42.8% (46). The level of physical activity, measured in 2005-2010, has remained relatively unchanged up to 2018 (46).

The prevalence of regular smoking in Greenland is remarkably high compared to Europe (22%) and, in particular, the Scandinavian countries (8-17%) (7). Although the quantity of cigarettes consumed daily by Greenlandic smokers may vary, no level of smoking is considered safe. Consuming even one cigarette a day is believed to induce half the CVD risk of a 20-cigarette-per-day smoker (50). High smoking rates are also observed among Indigenous populations, such as Aboriginals in Australia, Maori in New Zealand, First Nations in Canada, and American Indian and Alaskan Natives in the US, especially when compared to their non-Indigenous counterparts (51). A review of factors influencing smoking among young Indigenous people in these regions shows similarities with other populations. These factors include smoking habits within families, community norms, and individual issues like stress, as well as environmental elements such as socioeconomic status and family structure (51). This combination of familial, social, individual, and

environmental factors underscores the necessity for holistic and culturally sensitive strategies in smoking prevention and cessation, specifically tailored to the situations of Indigenous youth.

Regarding the clinical risk factors, there has been a marked increase in hypertension. The proportion of individuals with blood pressure above 130/80 mmHg or those on antihypertensive medication rose from 49% in men and 34% in women in 2005-2010, to 76% and 61% in 2018, respectively (46). Obesity rates, based on a body mass index (BMI) above 30 kg/m^2, have increased, from 13% in 1993 to 27% in 2018 (46). Low-density lipoprotein (LDL) cholesterol levels, measured in 2018, averaged 3.5 mmol/L, showing no difference between genders (46). The prevalence of diabetes was assessed by glycated hemoglobin (HbA1c) and oral glucose tolerance test (OGTT), in 2018, and there is considerable disparity in the results depending on the measurement. Among those above 35 years, the prevalence was between 6.2% and 18%, OGTT among men showed the highest prevalence (46). In 1999-2001 the prevalence, assessed only by OGTT among those aged above 35 years was 9.7% (52).

Psychosocial factors have also been an aspect of the surveys. Cohorts from the 1970s and 1980s reported a high incidence of individuals who had experienced violence, alcohol-related problems, or sexual abuse during childhood (46). These incidences have nearly halved among the 1995 cohort. The suicide rate has remained stable since the 1970s (46). The survey in 2018 included additional measures on mental health such as anxiety and depression, however, these results are yet to be published (46).

Genetic studies have identified specific genetic variants endemic to the Greenlandic Inuit. These genetic markers are associated with an increased risk of diabetes, obesity, familial hypercholesterolemia, and more generally, cardiovascular disease (53–56). For instance, a variant in the *TBC1D4* gene, common among the Greenlandic Inuit, is involved with glucose uptake in the muscle and is estimated to account for one in ten cases of diabetes in Greenland (54,57). Additionally, a newly identified variant in the *HNF1A* gene, although less frequent than the TBC1D4 variant, is associated with a fourfold increase in diabetes risk and has a significant impact on diabetes risk in the population (56,57). Furthermore, a variant in the *LDLR* gene, prevalent in 29.5% of the Greenlandic population, has been linked to high levels of LDL-cholesterol in carriers, subsequently increasing the risk of CVD (53).

Cardiovascular disease in Greenland

The history of cardiovascular disease, particularly atherosclerosis, in Greenland has been marked by evolving perceptions, grounded in both empirical research and anecdotal observations. The initial chronicles related to cardiovascular health in Greenland can be traced back to the 1940s. Albert Berthelsen,

a physician who dedicated several years to medical practice in Greenland, posited that atherosclerotic manifestations were not uncommon among the Inuit in Greenland (58).

Later, during the 1970s, a significant shift in the narrative emerged. The Danish researchers, Dyerberg and Bang, examined the typical diet of the Greenlandic Inuit. They were informed of a low or nearly non-existent incidence of myocardial infarction (MI) within the population, which was published, and attributed to the high intake of marine fats (59–62). However, this observation was later challenged. A comprehensive review in 2003 by P. Bjerregaard and colleagues, which incorporated 18 diverse studies delving into IHD and arteriosclerosis among the Inuit, postulated that the reported diminished incidence of IHD might have been affirmed upon less robust mortality statistics. Interestingly, their findings also underscored that stroke mortality rates among the Inuit were congruent with, if not exceeding, those observed in other global populations (63). Reinforcing this perspective, a 2014 review by Fodor et al. thoroughly evaluated the suggested absence of coronary artery disease (CAD) among the Inuit through the years. They concluded that CAD prevalence among the Inuit was similar to other global populations, and interestingly, they highlighted a disproportionately elevated stroke mortality (64).

Recent findings indicate a significant increase in the intake of refined carbohydrates and sugar, paralleling the rise in atherosclerotic disease in both Greenlandic and Alaskan Inuit (65,66). The traditional diet, which consisted of 2-8% carbohydrates and minimal refined sugar, shifted dramatically by 1955, with carbohydrate intake rising to 39% of total calories. Refined sugar intake also increased almost 30-fold from 1855 to the 1970s (65). This drastic dietary change, marking a departure from the traditional, healthier diet, may likely have contributed to the increased incidence of atherosclerosis, challenging previous perceptions of CVD among Greenland's indigenous population.

Contemporary research supports the conclusion made in the reviews, suggesting that IHD prevalence among the Inuit in more recent times, is comparable with trends observed in other Western demographics (67,68). Recently, the yearly rate of revascularization among Greenlanders was found to be at least as high as that among the Danes (69). Furthermore, the prevalence of atrial fibrillation in Greenland based on registered diagnose and treatment is comparable to other western populations and the incidence rate of ischemic stroke is comparable to the global rate (70–72).

Cardiovascular disease in Greenland has been subject to different notions. The history and genetic makeup of the Greenlandic population, along with a change in lifestyle and risk factors, have predictably led to changes over time. Given Greenland’s small population and finite resources, research is essential to elucidate the incidence and prevalence rates of disease. Understanding theses rates is necessary to guide healthcare strategies and the allocation of resources, thereby promoting the health of the population.

Healthcare in Greenland:

Greenland's 2.200.000 km² area is home to about 56,000 inhabitants, predominantly of Inuit origin, living in 17 towns and 56 settlements. The geographical constraints necessitate travel by plane, boat, or helicopter for access to healthcare, heavily influenced by weather conditions. Nuuk, the capital, is the most populated city, housing approximately a third of the national population. Greenland is part of the Danish Kingdom but has self-government and has gradually taken over administration with various departments. Today Greenland manages its healthcare system and has been doing this since transitioning from Danish control in 1992. The healthcare system is publicly funded, offering free healthcare services, including medicine and dental care.

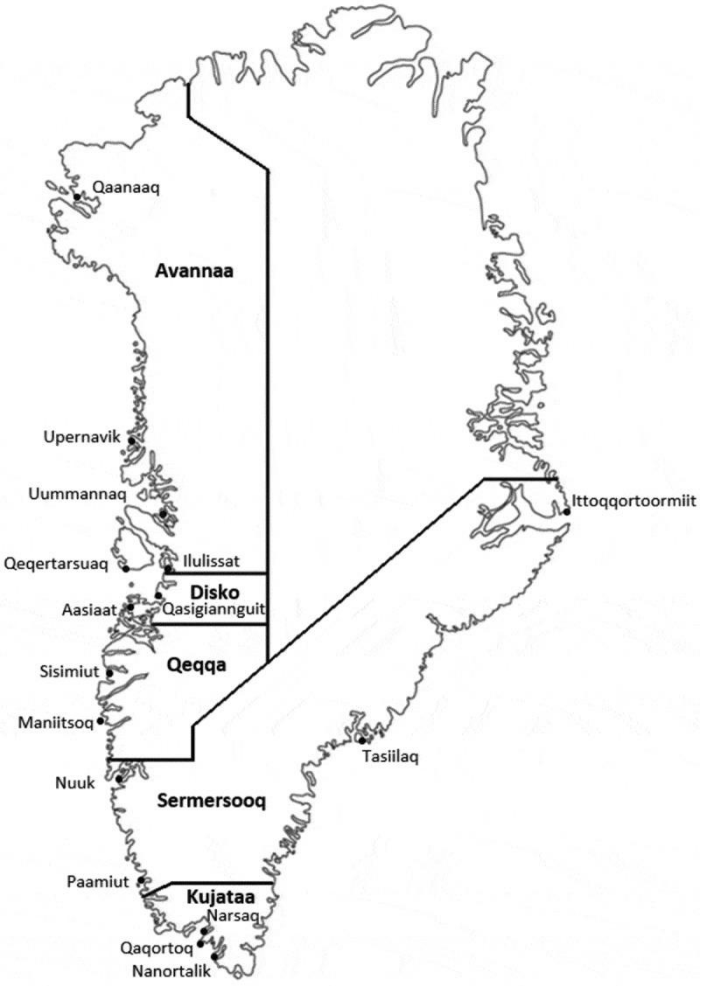

Figure 2. The five healthcare regions of Greenland (34).

Since undergoing a reform in 2010 the Greenlandic healthcare system has been structured into five regions. The reform was intended to address administrative and health professional challenges. However, challenges with employment continue to exist, especially in the less populated towns and settlements (48). Notably, the healthcare services in some areas are worsening and contributing to people moving from smaller areas to more populated cities (48). Today more than 60% of Greenlanders live in the 5 largest towns, which each contain a regional hospital. Around 25% of the population lives in places with healthcare centers, and most individuals in the remaining 55 settlements have access to a healthcare station (48,73).

The symptomatology of CVD varies depending on the degree and location of onset. Symptoms can range from sudden cardiac arrest or a severe stroke to mild arrhythmia or gradually presenting angina. Given the diversity in healthcare accessibility and travel possibilities, the outcome for the individual CVD patient

depends not only on the onset of the disease but also on geographical factors, as treatment options and medical expertise vary by location.

Study I:

Study I examine the incidence of registered CVD in Greenland, focusing on the period from 1994 to 2021. This research tries to provide a profile of CVD, investigating the incidence patterns among the Inuit population in Greenland.

Aim:

This study aimed to analyze the incidence and mortality rates of CVD among the Inuit of Greenland, addressing a gap in contemporary research and historical data. This investigation sought to provide a detailed epidemiological insight into CVD, focusing on IHD, stroke, heart failure, and atrial fibrillation/flutter (AF/AFL). By describing the trends and shifts in these rates, we hope to contribute to the global understanding of CVD in Arctic indigenous populations and inform healthcare and preventive strategies in Greenland.

Methods:

The study was a retrospective observational analysis based on data from Greenland's Hospital Discharge Register (GHDR) and Electronic Medical Record (EMR). The GHDR, operational since 1987, records discharge diagnoses, which are validated for epidemiological use in CVD research (74). The EMR, implemented between 2013 and 2017, captures both inpatient and outpatient diagnoses according to ICD-8, ICD-10, and the International Classification of Primary Care (75–77).

The cohort consisted of individuals fulfilling the inclusion criteria of being born in Greenland to Greenland-born parents and residing with a registered address in the country from January 1, 1994, to December 31, 2020. This period allowed for a comprehensive examination of CVD trends over nearly three decades. For those who met these criteria, additional study parameters such as birth, migration dates, and CVD diagnosis were included, using the Civil Registration Number for data linkage. Time spent outside Greenland was excluded from the analysis. CVD diagnoses were classified into subgroups: IHD, MI, stroke, HF, and AF/AFL. For each diagnosis, only the earliest record per individual in a subgroup was considered. We established gender-specific cohorts based on CVD subgroup diagnoses and created Lexis objects for each, allowing us to integrate data across age, calendar year, and follow-up duration. Our analysis relied on Poisson regression models that factored in age at diagnosis and the year of diagnosis, enabling us to predict CVD incidence rates across various age groups. Additionally, we compared CVD-related mortality risks, paying special attention to variations across genders and ages. We assessed model linearity and adjusted for deviations by segmenting the time variable. This methodological approach provided a framework for understanding CVD incidence and mortality trends in Greenland's Inuit population. The study's ethical adherence was approved by the Greenlandic Science Ethics Committee and conducted in accordance with the Helsinki Declaration.

Results and discussion:

The study included 65,824 participants. We analyzed an average follow-up duration of 18.9 years, amounting to a total of 1,242,053.5 person-years. The incidence rates of CVD across subgroups and mortality rates of CVD are presented and discussed in the subsequent sections.

Ischemic Heart Disease and Myocardial Infarction

From 1994 to 2021, there was a decline in IHD incidence rates among both genders in Greenland, with a more pronounced decrease in women. Men consistently showed higher incidence rates across all age groups. As age advanced, incidence rates for both sexes rose, peaking at age 80, although with a notably small difference between the oldest age groups (70- and 80-year-old).

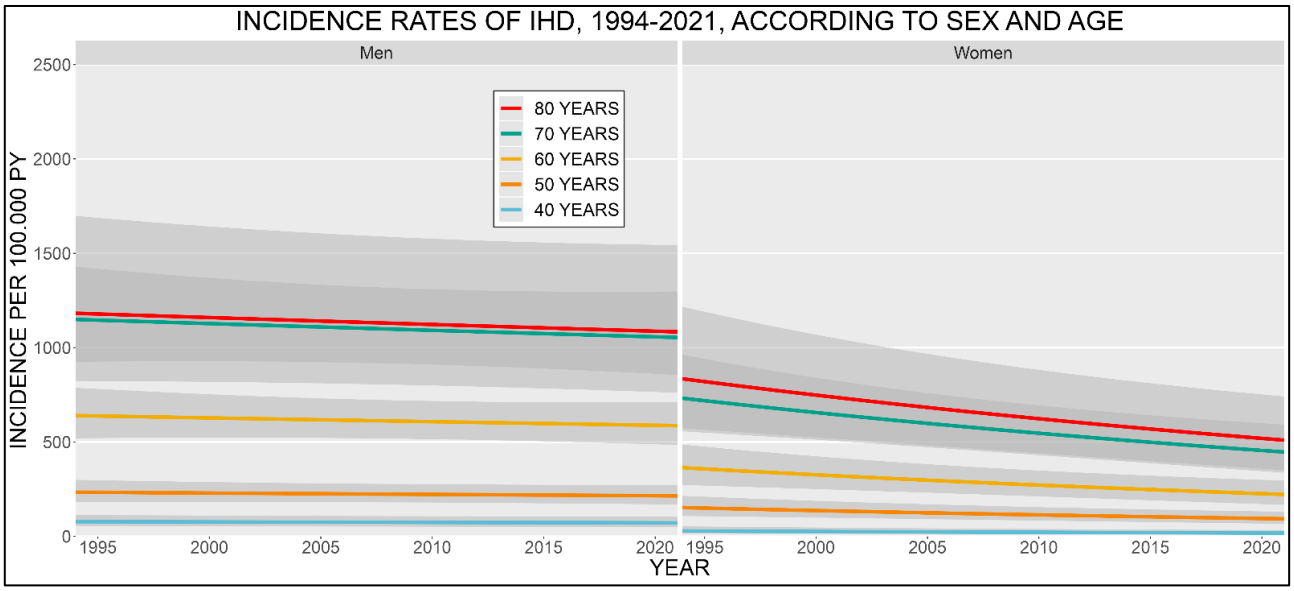

Figure 3. Incidence rate of ischemic heart disease per 100,000 person-years between 1994 and 2021, according to sex at age 40, 50, 60, 70, and 80 years. The shaded area shows 95% confidence interval. PY = person-years, IHD = ischemic heart disease.

Comparatively, the decline in Greenland's IHD rates mirrors global trends, which may reflect enhanced prevention efforts and improved management of risk factors like smoking, hypertension, and diabetes. Despite the overall decrease, the minimal difference in IHD incidence between the 70- and 80-year-old age groups suggests a 'healthy survivor' effect. This phenomenon indicates that the oldest individuals, particularly those aged 80, may inherently be healthier, as those more susceptible to IHD likely developed it at a younger age. Consequently, this results in a relatively stable IHD rate among the oldest age groups. We hypothesize that the lower IHD incidence found in this study, when compared to global estimates, might indicate underdiagnosis, especially given the similarities in revascularization rates with Denmark (69).

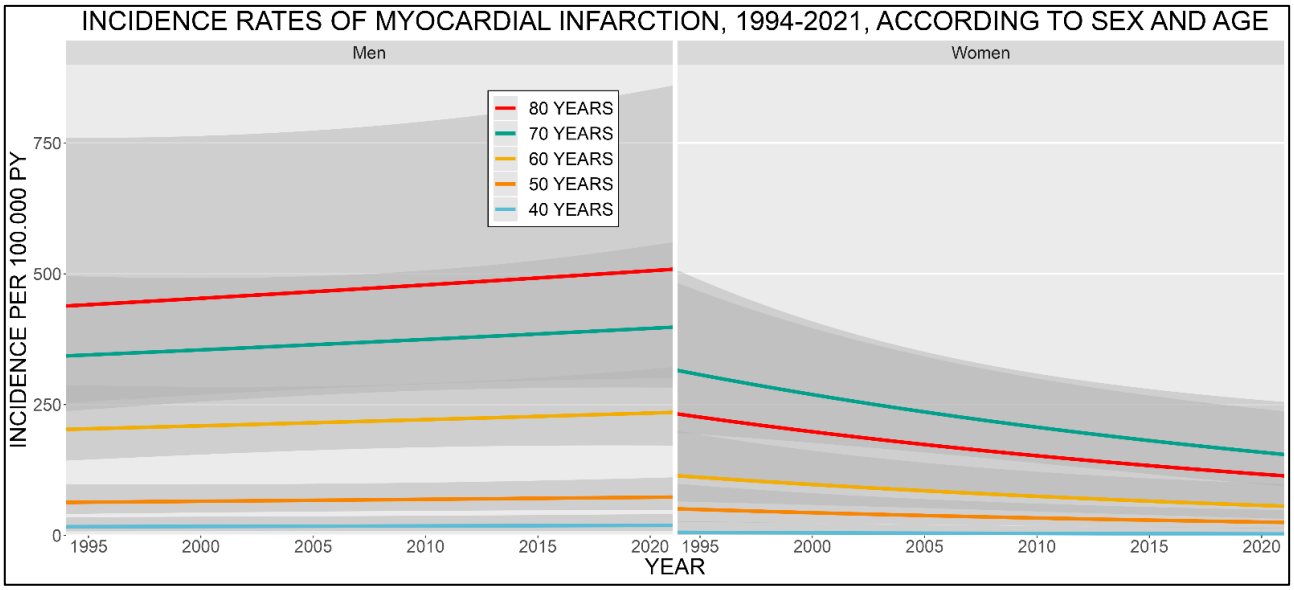

Figure 4. Incidence rate of myocardial infarction per 100,000 person-years between 1994 and 2021, according to sex at age 40, 50, 60, 70, and 80 years. The shaded area shows 95% confidence interval. PY = person-years.

For MI, the trend diverged; while women experienced a decrease in incidence rates, men showed an increase, deviating from patterns seen in most European countries (7,72,78). MI was specifically analyzed as a distinct category in the study due to its definitive diagnostic criteria. Unlike other forms of IHD, which can present with a range of symptoms and severities, MI is typically identified by clear, objective clinical markers. This distinct categorization helps in reducing potential uncertainties associated with diagnosing other IHD subtypes. We hypothesize that MI is less likely to be underdiagnosed in the Greenlandic setting, providing a more reliable measure for studying trends in heart disease within the population. MI showed a trend in men aligning more closely with Danish data (78). This divergence in MI incidence among men from global declining trends could indicate distinctive health dynamics within the Greenlandic population.

Stroke:

The IR of stroke in Greenland exhibited an overall decline, with a more substantial decrease observed in women. At the ages of 40, 50, and 80, women exhibited higher incidence rates, with the 80-year-old age group experiencing the highest rates. Across both sexes, the IR of stroke increased with advancing age.

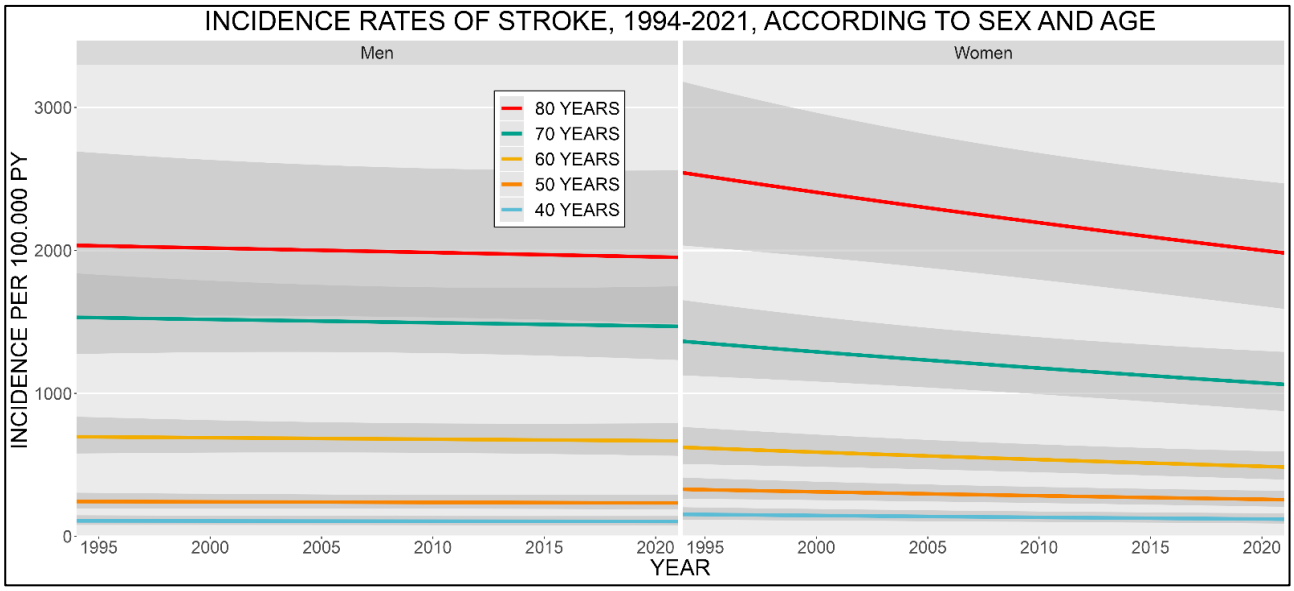

Figure 5. Incidence rate of stroke per 100,000 person-years between 1994 and 2021, according to sex at age 40, 50, 60, 70, and 80 years. The shaded area shows 95% confidence interval. PY = person-years.

Comparatively, the stroke IR in this study is significantly elevated, particularly in the older age groups, exceeding global averages by about 60% for the 40-80 age range (72). This elevated incidence does not seem to be explained by an unexpected contribution from various stroke subtypes like hemorrhagic and transient ischemic attacks but necessitates further investigation due to the potential complexity and diversity of stroke diagnoses.

Interestingly, the IR of stroke in Greenland surpasses that of IHD, a contrast to the typical pattern observed in other populations where IHD is more prevalent (7,79). This distinct pattern in Greenland may be attributable to an interplay of factors, including lifestyle and environmental risk factors that are more prone to cause stroke. Evidence from other cohorts has demonstrated specific associations between certain risk factors and types of CVD. For instance, elevated systolic blood pressure has been identified as a significant risk factor for ischemic stroke, whereas low-density lipoprotein cholesterol (LDL) shows a stronger association with coronary artery disease (CAD) (4). Suggesting that the high stroke incidence in Greenland could be influenced by the predominant presence of stroke-specific risk factors in the population. Additionally, a unique genetic predisposition among the Greenlandic Inuit, shaped by their historical isolation and a small ancestral gene pool, might also contribute to this specific disease pattern. Such genetic factors could potentially influence the differential impact of common CVD risk factors, further shaping the distinctive cardiovascular health landscape in Greenland.

The declining trend in stroke incidence rates in Greenland aligns with trends observed in many European countries, which somehow may reflect effective prevention and improved treatment of risk factors as seen in other populations (2,3,7). However, the gender-specific incidence revealed a more pronounced decrease in women, leading to more equal IR between men and women by the end of the study. The IR among men exhibited a negligible decrease, barely visible in the data. The gender-specific trend in stroke incidence, particularly among the elderly, reflects global patterns and raises questions about potential underlying causes, including different risk profiles or survivorship effects in older populations.

Heart failure

Greenland experienced a notable decrease in HF IRs, especially pronounced among women. The reduction in women's HF IR was remarkable, with approximately a fivefold decrease. The highest incidence rates were seen in the 80-year-old age group for both genders. This trend of decreasing HF IR is consistent with other populations, though the magnitude of change in Greenland was more significant.

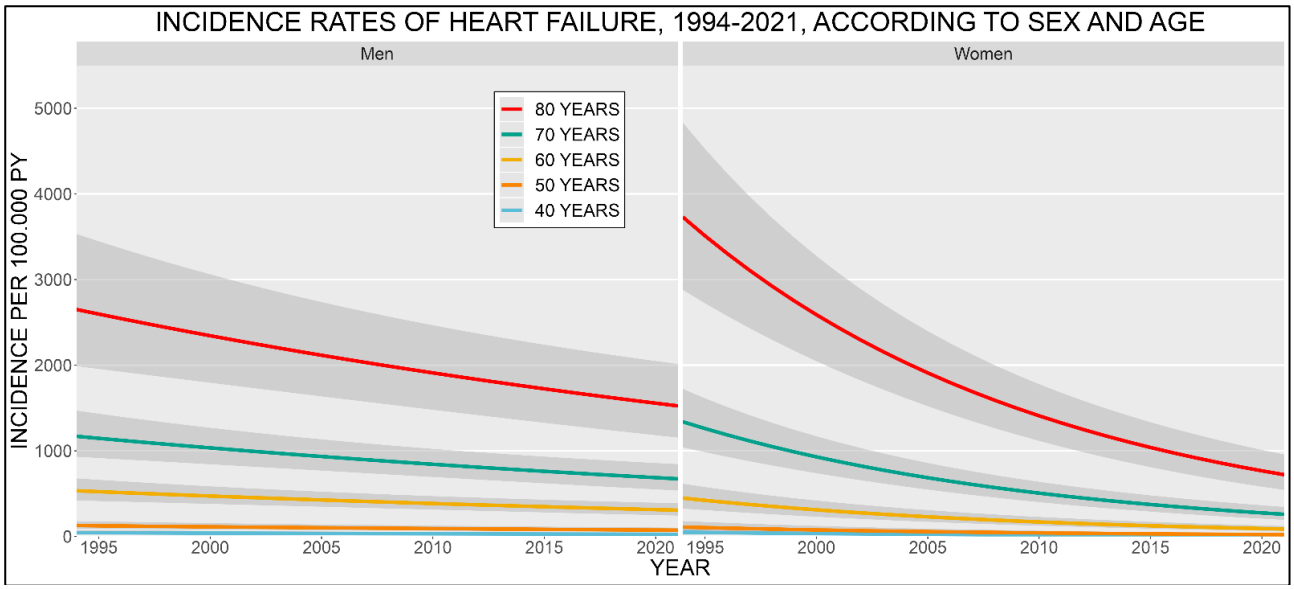

Figure 6. Incidence rate of heart failure per 100,000 person-years between 1994 and 2021, according to sex at age 40, 50, 60, 70, and 80 years. The shaded area shows 95% confidence interval. PY = person-years.

The early period of the study reported unusually high HF IR, suggesting potential issues with overdiagnosis or diagnostic inaccuracy at that time. Symptoms such as breathlessness and ankle swelling, typically associated with HF, might have been misinterpreted, leading to an overestimation of HF cases. Over the years, diagnostic criteria and understanding of HF have evolved, as evidenced by the first guidelines published by the European Society of Cardiology in 1995 (80). The advancement in knowledge and improvements in diagnostic opportunities may explain the decline, as the criteria become more concise, especially given the Greenlandic setting with sparsity in specialized health care workers. Additionally, the focus on HFrEF might have led to the under-recognition of HFpEF, which has been found to represent a

significant proportion of HF cases (81). Improved healthcare overall, including better management of HF risk factors like hypertension and IHD, and a reduction in diseases like rheumatic heart disease that contribute to HF, also likely played a role in the declining HF IR observed in Greenland (22,82).

Atrial fibrillation/flutter

During the study period, there was a discernible increase in the IR of AF/AFL among both men and women in Greenland. Notably, women aged 80 years exhibited the highest IR, while at all other age levels, men showed higher IRs. This upward trend in AF/AFL IR contrasts with the stable rates observed globally and in Europe (7,72).

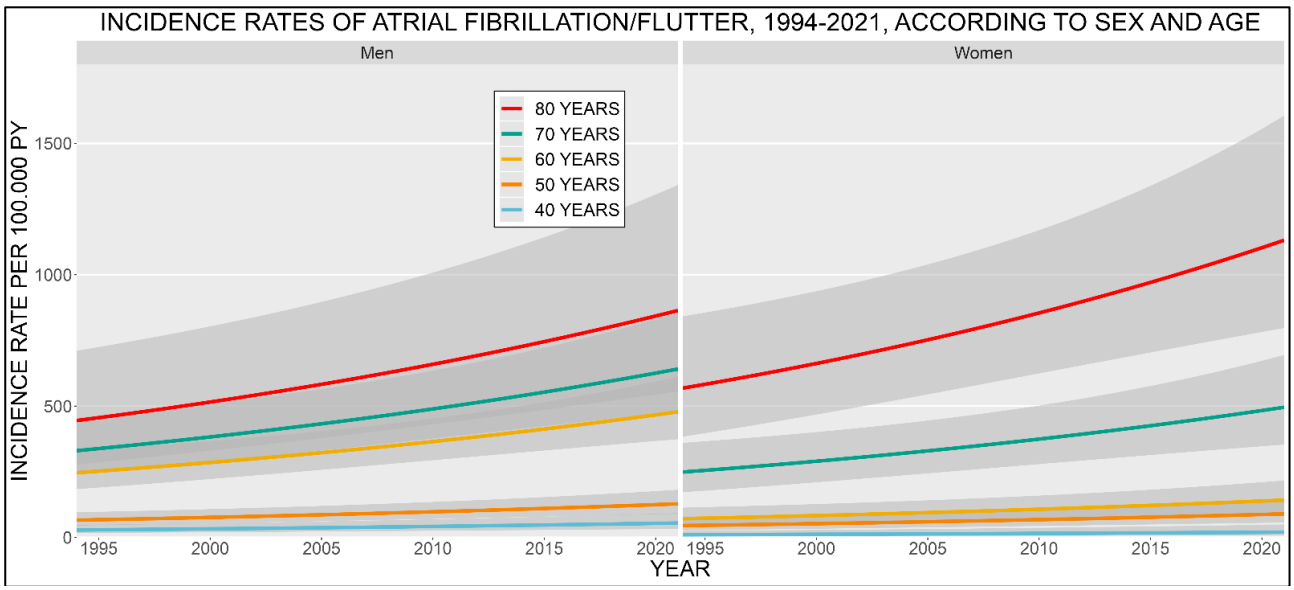

Figure 7. Incidence rate of atrial fibrillation/flutter per 100,000 person-years between 1994 and 2021, according to sex at age 40, 50, 60, 70, and 80 years. The shaded area shows 95% confidence interval. PY = person-years.

The IRs in Greenland at the start of the study were on par with global figures but escalated significantly towards the end, markedly higher than the global estimates of 2019, but comparable to the Danish estimates in 2018 (83,84). This increase in AF/AFL IR could be attributed to advancements in diagnostic methods, such as the more widespread use of Holter monitoring devices. Additionally, the prevalence of risk factors like hypertension, diabetes, HF, IHD, and obesity might also have contributed to the rise in AF/AFL cases (85). While AF/AFL is generally more common in men globally, the data from Greenland indicates a similar pattern except among the oldest demographic, where women had the highest IR.

Mortality

Within the study's timeframe, there were 11,623 total deaths, with 2,941 occurring in individuals diagnosed with CVD. The median age of death was 66.5 years.

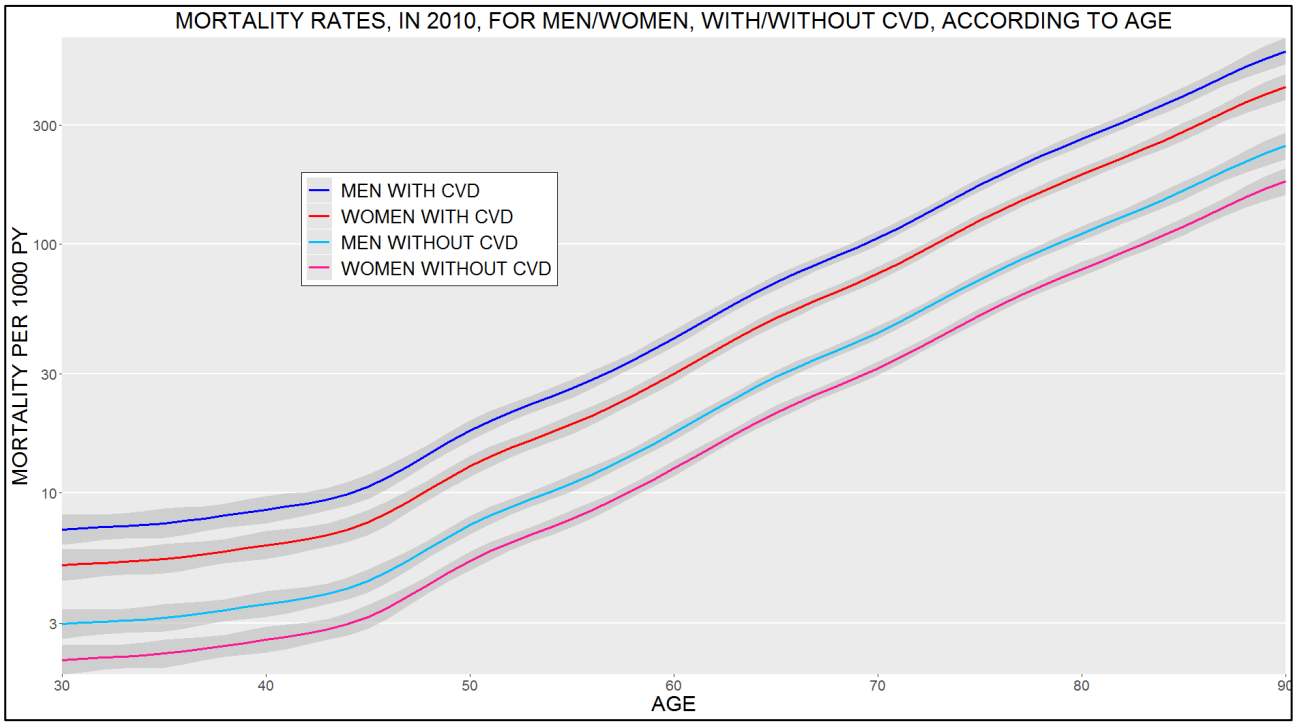

Figure 8. Mortality rate for men/women and with and without cardiovascular disease, based on mortality rates in 2010. The y-axis representing the mortality rate is on a logarithmic scale. The shaded area shows 95% confidence interval. The mortality rate ratio for cardiovascular disease: 2.4, and for Male sex: 1.4. PY = person-years, CVD = cardiovascular disease.

Those with a CVD diagnosis exhibited a mortality rate ratio of 2.4, indicating a significantly higher risk of death compared to those without CVD. Notably, the overall mortality rate ratio was higher for men, standing at 1.4 times that of women. This gender disparity in mortality rates is aligned with findings observed in other population studies (86). The rates underscore the heightened mortality risks associated with CVD and emphasize the importance of enhanced prevention measures, particularly focused on the male population.

The overall burden of cardiovascular disease

To assess the impact of CVD on the healthcare system, considering demographic shifts, crude unadjusted incidence rates were computed. During the study period, the unadjusted incidence rates of stroke, IHD, and AF/AFL witnessed an upward trend. Stroke, notably, registered the highest unadjusted incidence rate among these. In contrast, the unadjusted incidence rate for HF showed a decline. These unadjusted incidence rates

provide a crucial perspective on the CVD burden within different subgroups.

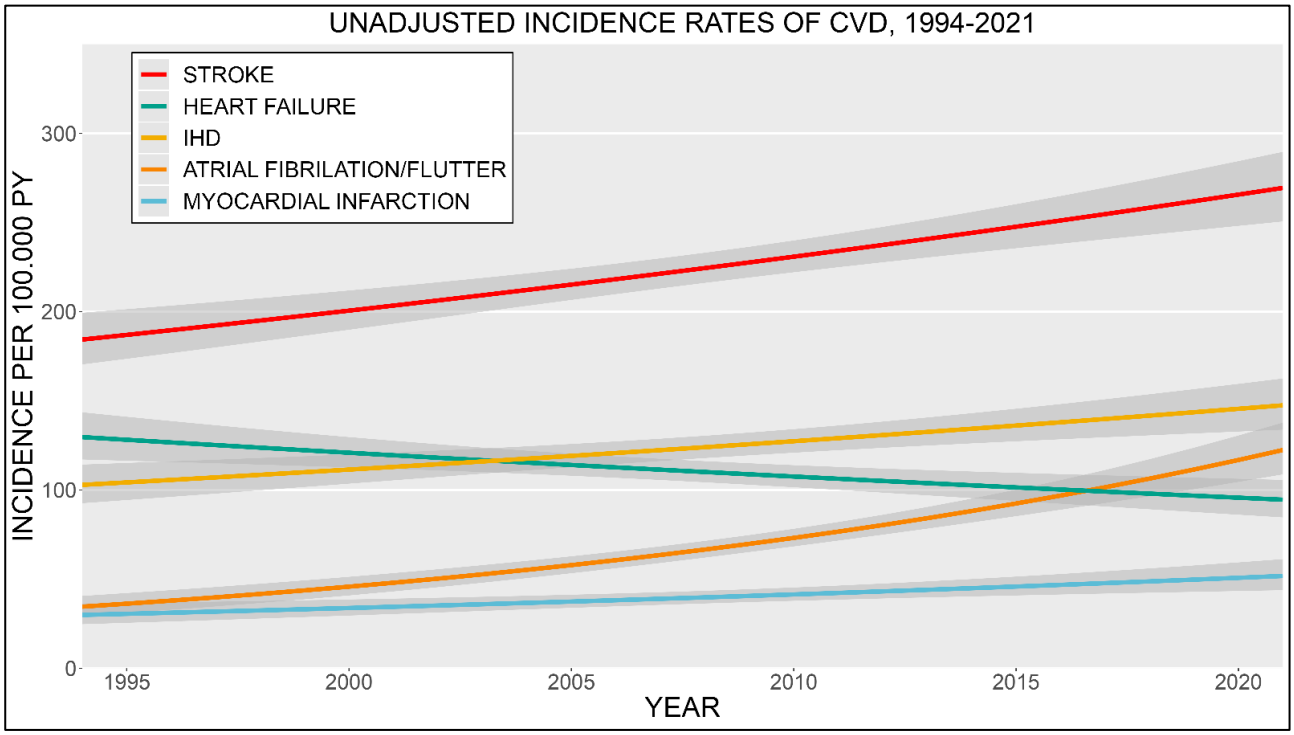

Figure 9. Unadjusted incidence rates of cardiovascular disease according to subgroup per 100,000 person years between 1994 and 2021. Shaded area shows 95% confidence interval. PY = person years, CVD = cardiovascular disease, IHD = ischemic heart disease.

With the global rise in life expectancy, the proportion of the elderly population, particularly prone to CVD, has increased. This trend is mirrored in Greenland, where the population over 60 years of age has doubled since 1994 (87). Such demographic changes have led to an expected increase in the unadjusted incidence rates of IHD, MI, stroke, and AF/AFL, with stroke emerging as the most prevalent. The decline in the unadjusted incidence rate of HF aligns with the observed decrease in its age- and sex-specific incidence rates. The growing incidence of CVD among Greenland's aging population presents substantial challenges for the healthcare system, necessitating enhanced public health efforts. The high incidence rate of stroke is particularly concerning and underscores the need for focused strategies to address the unique risk factors and healthcare needs of the Greenlandic population. Emphasizing primary prevention is crucial in mitigating the development of modifiable risk factors associated with CVD, such as tobacco smoking, obesity, dyslipidemia, hypertension, hyperglycemia, poor diet, and physical inactivity from an early age (88). The increasing prevalence of obesity in young children and the commonality of daily smoking in Greenland highlight the need for comprehensive societal interventions (46,89). These could include health education, promoting access to healthy food options, encouraging physical activity, and enhancing healthcare access. Continuous research and monitoring of CVD and its risk factors are essential for guiding intervention strategies and assessing their effectiveness in the Greenlandic context.

Limitations

In our study, we utilized nationwide registers to capture a comprehensive picture of the Greenlandic population. This method ensures a robust representation, yet it must be acknowledged that, given Greenland's unique healthcare context characterized by remote and sparsely populated areas, the true incidence of CVD might be higher than what our data suggests. This potential underestimation is an important consideration in understanding the landscape of CVD in Greenland and in shaping future public health initiatives.

Moreover, given the healthcare system's limitations in such a geographically challenging and thinly populated region, there's a plausible risk of underdiagnosis, which could skew the incidence rates of CVD. Therefore, it's imperative to continue research and monitoring of CVD prevalence and risk factors in Greenland. Such ongoing efforts are crucial for accurately assessing the healthcare needs of this unique population and for implementing effective public health strategies tailored to Greenland's specific context.

Perspectives:

Study I provides insights into CVD in Greenland, contributing to the broader understanding of these conditions in Arctic populations. By drawing on extensive data from nationwide health registers, this study provides a more detailed and less biased analysis of CVD trends, moving beyond the limitations of earlier research. Our findings align with other contemporary research in suggesting that Greenland's CVD prevalence is more closely with global trends, challenging older, perhaps outdated narratives.

We observed varied epidemiological patterns of CVD among the Inuit with notable increases in AF/AFL and MI among men pointing to changing health challenges, potentially linked to lifestyle shifts and population demographics. These findings call for adaptive public health policies and further research to monitor these evolving trends. The decreasing trend in age-adjusted CVD incidences, despite the rising prevalence of risk factors like hypertension, obesity, and diabetes, suggests that Greenland's strategies for managing these risks may be effective. The slight decrease in smoking prevalence, although still high, may also contribute to this positive trend.

The contrast between decreasing and rising incidences in different CVD subtypes underscores the need for a nuanced approach to healthcare, considering both the dynamic nature of these conditions and the limitations inherent in the data sources. The reliance on registers, which may carry uncertainties due to the small number of cases and logistical challenges, necessitates cautious interpretation. To enhance future research and monitoring of disease prevalence, as well as the effectiveness of treatment and prevention strategies, maintaining the quality and reliability of these health registers is critical. Establishing a dedicated

CVD register in Greenland could significantly improve research capabilities, providing precise data for informed healthcare planning and policy-making.

This research contributes to the global discussion on CVD, especially in indigenous and remote populations, challenging existing paradigms. It emphasizes the importance of continuous research and dialogue among healthcare professionals, policymakers, and communities to develop effective prevention and management strategies for CVD. The study advocates for robust, flexible healthcare systems in Greenland and represents a vital step towards a more inclusive public health approach, recognizing the unique characteristics of Greenland's population and the importance of timely, evidence-based action.

Contributions:

I played a role in conceptualizing the study alongside my supervisors. My primary contributions included establishing a collaboration agreement between the healthcare system and Greenland Statistics, securing ethical approval, and obtaining authorization from the healthcare administration. I was responsible for the statistical analyses, creating figures and tables That were central to our research outcomes. Additionally, I authored the initial draft of the research paper, representing our results and interpretations and I managed subsequent revisions, and submission.

Study II:

Study II shifts focus to the specific cardiovascular condition of HF in Greenland. The study investigates the prevalence and clinical characteristics of HF among the Greenlandic population, trying to enhance the understanding of HF within the unique environmental and genetic context of Greenland.

Aim:

Study II was conducted to estimate the prevalence of HF in Greenland and to explore its clinical characteristics, focusing on pathology and local risk factors like smoking, obesity, and diabetes. Our goal was to uncover the nature of HF in this population, aiding in the development of targeted healthcare interventions.

Method:

In Study II, we included all patients identified with an HF diagnosis in the EMR. We extracted the latest data on demographics, physiological measurements, and cardiac function indicators such as LVEF. BMI was computed and categorized into standard weight classes. LVEF was classified into three categories (HFrEF, HFmrEF, HFpEF) based on established criteria. We also included recent blood test results and information on diabetes and IHD based on EMR diagnoses.

For statistical analysis, the prevalence of HF was calculated from the total Greenlandic population aged 16 and above as of January 1, 2022. We employed a binomial generalized additive model for visualizing HF diagnosis in relation to age, separately for men and women. The continuous effect of age was examined using a binomial generalized linear model. For international comparisons, data was segregated by sex and age groups, with prevalence rates and confidence intervals calculated for each.

Patient characteristics were analyzed based on sex and IHD diagnosis. Continuous variables were evaluated for distribution and presented as mean and standard deviation or median and interquartile range, as appropriate. Statistical comparisons across sex and IHD groups utilized Fisher's exact test, Pearson's Chi-squared test, and Welch's Two Sample t-test.

Results and discussion:

In Study II, we identified 507 HF patients, excluding three under 16. The overall HF prevalence in Greenland was 1.1%, higher in males, and increased with age. The highest prevalence was in men over 85. Continuous age analysis showed a significant association with HF. The study revealed notable characteristics: the mean age of HF patients was 64.9 years, with a high percentage of daily smokers (43%) and obesity prevalence (53%). About a quarter had diabetes, and a third had IHD, more common in men.

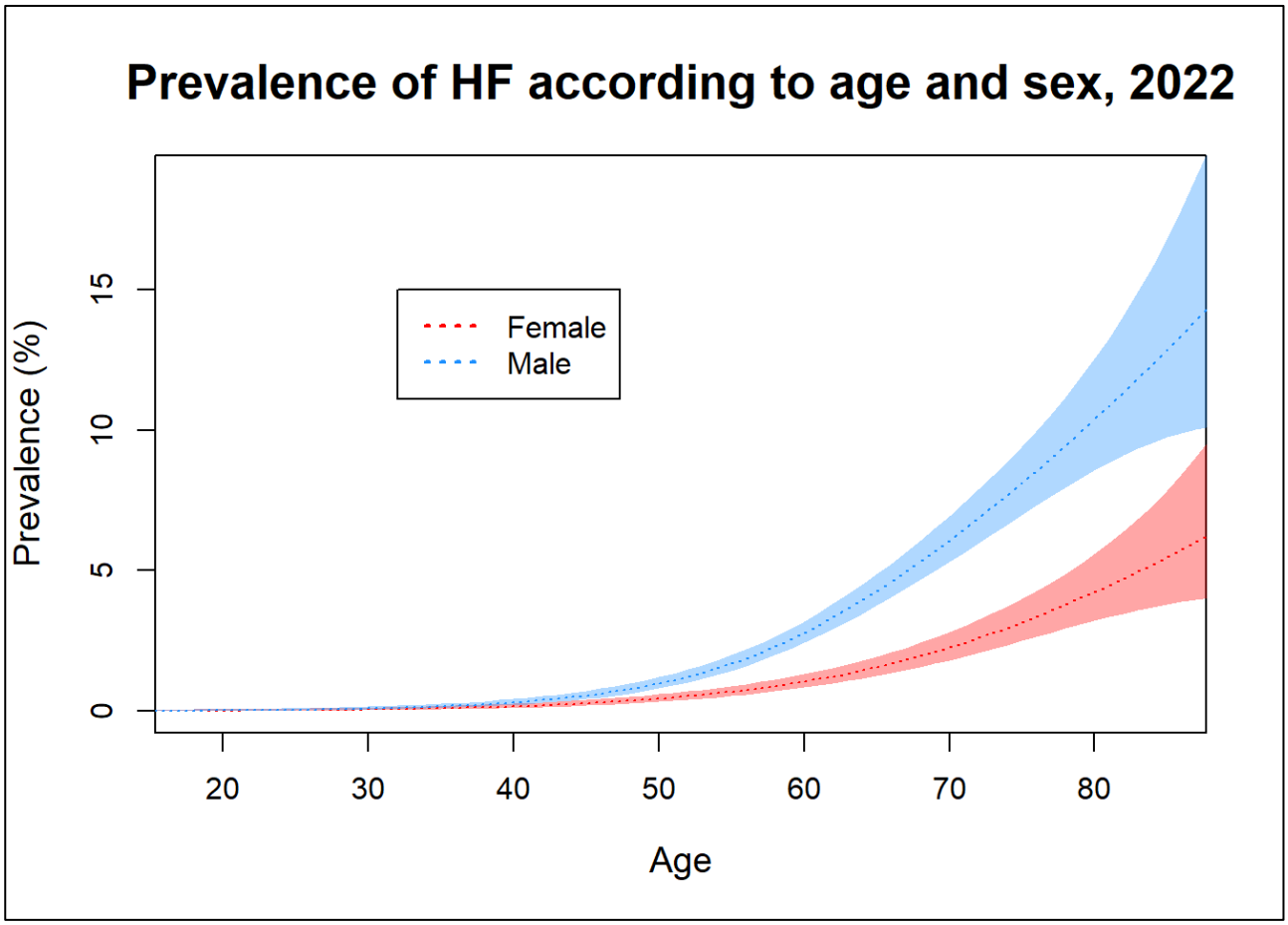

FIGURE 10. *Estimated prevalence of HF in Greenland, 2022, based on registered ICD-2 code and ICPC-2 code for heart failure in the EMR. Shaded area shows 95% confidence interval.*

Considering the prevalence of risk factors for heart failure (HF), we initially anticipated a high overall prevalence of HF in Greenland. However, our findings surprisingly indicate that HF prevalence in Greenland aligns with that of high-income countries (28,30,36). The lower-than-expected prevalence might be influenced by the shorter life expectancy, which reduces the proportion of elderly individuals who typically exhibit a higher prevalence of HF. Another factor potentially affecting our findings is a general challenge of underdiagnosing chronic disease in Greenland, as has been suggested for osteoporosis and psoriasis and hypothesized from the results of Study I (90,91). Furthermore, the limitations of the EMR, particularly the absence of data prior to its implementation, could also have contributed to our findings. Compared to Denmark, Greenland exhibits a higher HF prevalence in specific age groups, indicating distinct health challenges (92). This could be a factor in the lower life expectancy observed in Greenland. Comparative research shows a higher HF prevalence in similar indigenous populations: 5.14% among Métis in Ontario, Canada, and 6.4% in Nunavut for those aged 40+, compared to 1.22% and 2.04% in similar age groups in Greenland (93,94).

Interestingly, the proportions of HFpEF and HFmEF are higher than in Europe, possibly linked to obesity and diabetes prevalence. The lower IHD prevalence might be due to underdiagnosis or a different HF etiology in Greenland, potentially influenced by genetic factors.

Our study, the first to detail age- and sex-specific HF prevalence in Greenland, covered about 90% of the population, utilizing standardized data from the nationwide EMR. It's important to note that the reported prevalence reflects diagnosed HF cases, suggesting actual prevalence could be higher. Underdiagnosis, particularly of IHD, may have influenced results. HF patients outside Nuuk may be misdiagnosed due to limited diagnostic resources. Notably, our study did not include data on hypertension and other relevant comorbidities or treatments, which constitutes a limitation in comprehensively understanding HF in Greenland.

Perspectives:

In Greenland's healthcare landscape, characterized by remote and dispersed communities, maintaining a focus on HF and staying updated with diagnostic advancements is crucial. Given the increasing prevalence of obesity, hypertension, and diabetes, a rise in HF cases is anticipated. It seems imperative to adapt healthcare strategies not only to manage these growing risk factors but also to proactively prevent their further escalation. This involves continuously enhancing the awareness and understanding of HF among healthcare professionals, including adopting new and more efficient diagnostic tools as they become available, ensuring timely and accurate HF diagnosis. Such proactive and preventive measures in healthcare are key in adapting to the unique challenges of providing care in Greenland’s distinct geographical context.

While the current system is functional, continuously enhancing the awareness and understanding of HF among healthcare professionals is important. This involves being open to adopting new and more efficient diagnostic tools as they become available, ensuring timely and accurate HF diagnosis. Such an approach is key in adapting healthcare practices to the unique challenges of providing care in Greenland's distinct geographical context.

The unique genetic makeup of the Greenlandic Inuit may harbor specific variants associated with non-ischemic HF. Investigating this genetic aspect could yield insights into unique pathophysiological mechanisms, contributing to global knowledge in HF genetics and personalized treatment approaches. Moreover, deeper research into the roles of obesity, smoking, and IHD in the Greenlandic population is warranted. Understanding the interplay of these factors will guide more effective prevention strategies, benefiting both individuals and the broader society. This research could help form future healthcare planning, aligning with global trends while catering to local needs.

Contributions:

In Study II, I was involved with both the conceptualization of the study and its practical execution. I secured the necessary ethical approval and obtained authorization from the Greenlandic healthcare administration. A significant part of my contribution involved a quality review within the EMR, ensuring the accurate documentation of patients diagnosed with heart failure or receiving HF medication. Additionally, I authored the initial draft of the research paper, including creating integral figures and tables, and managed the process of revising and refining our findings.

Study III:

Study III builds on the findings in study II and investigates the genetics of people with non-ischemic HF.

Aim:

Study III aims to investigate the genetic underpinnings of DCM in the Greenlandic population, focusing on HF patients without IHD. This study addresses a gap in understanding the genetic landscape of DCM in the genetically distinct and historically isolated population of Greenland.

Methods:

We performed a clinical cross-sectional study, designed to screen HF patients in Greenland for both known and novel gene variants associated with DCM. The study encompassed Greenland's five healthcare regions, utilizing local healthcare facilities for patient examinations and blood sample collections. All HF patients diagnosed in the EMR were assessed for eligibility based on specific inclusion and exclusion criteria.

Patients aged 60 or under, diagnosed with HF, and exhibiting an LVEF of 40% or less were included. Exclusion criteria encompassed a history of IHD, primary heart valve disease, atrial fibrillation, structural congenital heart disease, prior chemotherapy, and diagnosed endocarditis. The study involved patient examinations, including standard procedures for height, weight, blood pressure measurements, electrocardiogram (ECG) assessments, and blood and urine tests. For genetic analysis, blood samples were processed for whole-genome sequencing (WGS) at the Novo Nordisk Foundation Center in Copenhagen. The study used a refined approach for WGS and variant calling, employing the PALEOMIX pipeline and other advanced bioinformatics tools for processing, mapping, and annotating genomic data.

A focused genetic screening was conducted on 44 genes linked to DCM, classified based on disease-specific metrics by the Clinical Genome Resource (ClinGen). Variant screening

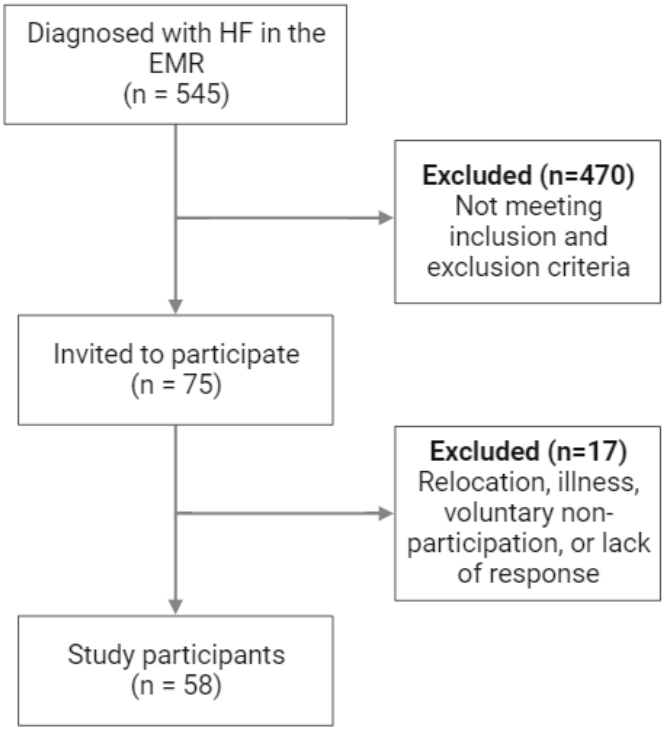

Figure 11: Participant recruitment flowchart outlining the progression from diagnosis with HF in the EMR to final study enrollment.

involved filtering WGS data for these genes, retaining variants with moderate to high consequences, and utilizing both dbSNP and ClinVar databases for variant classification.

The ethical considerations of the study were carefully addressed, securing approval from the Science Ethics Committee in Greenland, and adhering to the Helsinki Declaration. To ensure ethical compliance and respect for patient autonomy, all participants provided informed consent. Before commencing the study, I actively sought to engage with the Greenlandic community by attending a public meeting organized by the Greenlandic Heart Association. During this meeting, I presented our proposed study and solicited feedback on conducting a genetic study in Greenland. The response from the association's members was predominantly positive, and the concept of the study was well-received.

Results and discussion:

In our comprehensive study, we investigated 545 individuals diagnosed with HF in Greenland's EMR, out of which 58 met our rigorous inclusion and exclusion criteria. The participants, primarily male (61%) with an average age of 48.1 years, represented diverse geographical regions of Greenland.

Our genetic analysis revealed 4,234 variants in 19 genes strongly associated with DCM and an additional 13,016 variants in 25 genes with limited DCM association. Upon filtering, we identified 58 potentially functional variants in the former group and 52 in the latter. Notably, six and four variants, respectively, were previously unrecorded in the dbSNP database. Most variants were classified as benign or likely benign, with a minority as variants of unknown significance (VUS). A single likely pathogenic variant, MYH7 p.K637E, was discovered in two related individuals, marking a 3% positive prevalence of such variants in our cohort.

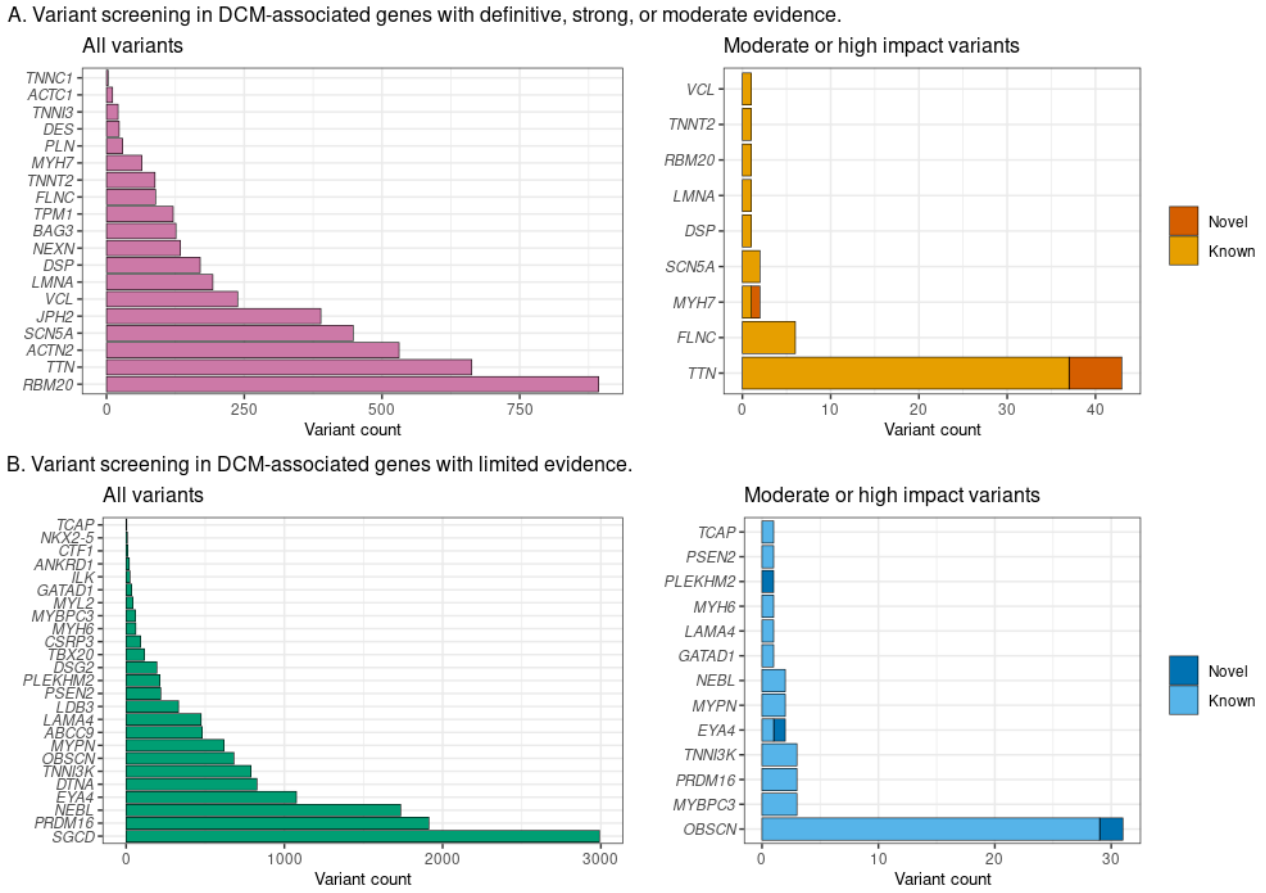

Figure 12: A) Screening of 19 genes curated for dilated cardiomyopathy variants classified with definitive, strong, or moderate, evidence with all identified variants in the left panel, and variants with a high or moderate predicted functional impact in the right panel. B) Screening of 25 genes with limited evidence of association with DCM with all identified variants in the left panel, and variants with a high or moderate predicted functional impact in the right panel. Novel variants are variants without a dbSNP id.

Contrasting with other cohorts, such as those in Denmark and America where the prevalence of pathogenic variants in DCM patients is markedly higher, our findings suggest unique genetic characteristics in the Greenlandic population (95–99). The ancestral isolation and genetic bottlenecks experienced by this population may have led to a distinct genetic landscape, potentially harboring novel or region-specific variants not captured by our gene panel. Mirroring our findings, a recent investigation into DCM among individuals of African descent revealed a similar disparity, these individuals are less frequently found to have actionable genetic variants in DCM-related genes, compared to their European counterparts. This difference is thought to stem from variations in genetic makeup and a scarcity of clinical and reference data that includes people of African ancestry (39). This is underscored by the discovery of the TBC1D4 variant, significant in Greenlanders but absent in other populations. Such findings emphasize the need for diversity in genetic research, especially considering the predominance of studies focused on European gene variants.

Our study did face limitations, including the potential inclusion of non-DCM patients and challenges in accurately categorizing DCM due to healthcare accessibility issues in Greenland. However, the strengths lie in our utilization of extensive EMR data and detailed clinical characterizations.

The identification of a substantial number of VUS aligns with broader research trends, underscoring the evolving nature of genetic interpretations. The unique MYH7 variant found in our study, though not cataloged in dbSNP, aligns with previous research indicating its pathogenic potential.

In conclusion, our study sheds light on the genetic underpinnings of DCM in the Greenlandic population, highlighting the importance of considering unique genetic and environmental contexts in genetic research. Future studies, potentially involving genome-wide analyses and larger cohorts, are needed to unravel the genetic architecture of DCM in this unique population.

Perspectives:

Study III's exploration into the genetics of DCM in Greenlanders indicates a distinct genetic landscape from European populations. The absence of commonly identified DCM-related genetic variants in the Greenlandic cohort suggests that novel molecular pathways/genetic associations may be implicated in DCM development in Greenland that the study could not account for, emphasizing the need for genetic discovery studies in Greenlanders and potentially genetic screening tailored to their genetic ancestry. The relative lack of positive genetic findings may also be indicative of a higher contribution of non-genetic factors in the development of DCM. Further research is necessary to confirm the absence of specific DCM-related genetic variants in this population. Understanding these genetic associations could significantly improve DCM treatment and prevention in Greenland. This knowledge gap somehow contributes to disparities in care for Greenlandic DCM patients compared to their European counterparts.

The findings necessitate a nuanced approach in clinical practice, particularly in cases of early-onset HF. While genetic testing remains a valuable tool, our research suggests that such tests in Greenland's population are less likely to yield a positive finding, limiting the utility of the screening. This outcome may stem from our current focus on genetic markers identified in populations with European ancestry, highlighting the need for broader genomic research to uncover potentially unique genetic factors in the Greenlandic genetic makeup related to DCM. Public health strategies might benefit from focusing on the modifiable risk factors in the prevention and treatment of HF, given the lack of identified genetic causes. Addressing known risk factors like hypertension and IHD becomes more pertinent in this context.

For future research, there is a clear direction towards more discovery-oriented genetic studies in Greenland. Genome-wide association studies or family-based analyses could uncover novel genetic variants associated

with DCM/HF, contributing significantly to our understanding of heart failure in unique genetic populations. Carrying out these types of genetic studies in Greenland has both benefits and challenges. On the one hand, the relative lack of genetic diversity and extended linkage disequilibrium pattern in Greenlanders increases the statistical power of the genetic association study. On the other hand, the small total size of the population offers limited power when studying a relatively rare disease such as DCM (100).

Ethically, it's essential to approach all research, but especially genetic research in indigenous populations with deep respect for the participants and the broader Greenlandic community. Sharing results and leveraging findings to improve public health and healthcare systems is vital. Our study's ethics focused on respect, collaboration, and cultural sensitivity. The project commenced after positive feedback from the Greenlandic Heart Association, ensuring community support. Informed consent was pivotal, with all information provided in Greenlandic. The study aligns with the local cultural context, reflected in a prior qualitative study emphasizing the importance of providing the results to the participants and community (101). The potential findings in our study aimed to enhance Greenlandic healthcare, by helping in identifying individuals at high risk of DCM for early intervention.

Overall, Study III underscores the need for genetic diversity in medical research and highlights the importance of including underrepresented populations in genetic studies. This approach is crucial for uncovering potential new pathways for understanding and treating DCM, not just in Greenland but globally.

Contributions:

In Study III, my role was practical and multifaceted. I obtained ethical approval and consent from Greenland's healthcare administration. I conducted a thorough assessment in the EMR for participant selection. My responsibilities included writing participant invitations, discussing the study and genetic testing with patients, and obtaining informed consent. I organized and conducted testing and blood sampling, except for blood and urine samples. The manuscript draft was my responsibility. Additionally, I collaborated with Novo Nordisk Foundation Center for Basic Metabolic Research who conducted the genetic analysis, gaining insights and learning from their expertise.

Concluding remarks:

The findings of this thesis are in line with what contemporary research has implied regarding the understanding of CVD in Greenland. Historically, since Dyerberg and Bang's influential studies, it was widely accepted that the Greenlandic population experienced a low incidence of CVD, a phenomenon attributed to their diet rich in n-3 fatty acids from marine mammals. However, our research reveals an existing and increasing trend in CVD, particularly among the elderly. The emerging health landscape of CVD challenges

the historical narrative, suggesting that the perceived low incidence may have led to an oversight in healthcare focus and research efforts over the years. This thesis underscores the need for a critical reevaluation of these beliefs, as they may have shaped healthcare resource allocation and the direction of epidemiological studies in Greenland.

The high prevalence of modifiable risk factors within the population, including smoking, obesity, hypertension, and diabetes, is a significant concern. Tackling these risk factors is crucial for better cardiovascular health outcomes. Implementing comprehensive public health campaigns that focus on the dangers of smoking, the benefits of a healthy diet, and regular exercise is necessary. Policy interventions, such as taxation on unhealthy foods and cigarettes, along with improved access to healthier lifestyle choices, could be effective. The development of community-based programs promoting physical activities, tailored to the Greenlandic culture and environment, can also play a vital role. Furthermore, strengthening primary healthcare services to provide regular screening and effective management of hypertension and diabetes is essential. Adapting the insights from genetic research into clinical practice presents another approach to tackling the challenge of increasing CVD. An example of this could be screening for the prevalent LDLR gene variant, for which well-established medical treatments are readily available. Continuous monitoring of the incidence and prevalence of these risk factors is crucial for adjusting healthcare strategies effectively.

Our investigation into the genetics of DCM in Greenlanders reveals a distinct genetic landscape from European populations. This may have implications reaching wider, suggesting the presence of unique genetic factors in Greenlanders that could be related to other diseases. Genetic research, while promising in revealing new disease mechanisms and potential treatments, must be approached with respect and ethical consideration. This research opens new avenues for understanding disease mechanisms and highlights the need for genetic diversity in medical research.

Future research and policy recommendations arising from this thesis include the need for ongoing epidemiological studies to monitor the changing trends of CVD in Greenland, especially among indigenous populations. The Greenland government should prioritize healthcare resources for CVD prevention and treatment, tailored to the unique needs of its population. Healthcare system reforms could be used to integrate robust CVD monitoring and management programs, with an emphasis on primary prevention. Expanding genetic research to include genome-wide association studies and family-based analyses will uncover novel genetic variants associated with CVD and DCM. Collaboration between local healthcare providers, international researchers, and policymakers is crucial to developing effective and culturally sensitive healthcare strategies.

In conclusion, this thesis enhances our understanding of CVD, HF, and DCM in Greenland and underscores the need for nuanced public health strategies, healthcare planning, and genetic research. It contributes to the global narrative on heart health prevention and management, highlighting the importance of evolving research methodologies to address health challenges in unique populations worldwide.

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Paper I:

Trends in cardiovascular disease among Inuit in Greenland from 1994 to 2021

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ABSTRACT:
Background and aims: Cardiovascular disease (CVD) poses significant health challenges globally. While substantial data exists for most populations, the Arctic Inuit's CVD incidence rates remain understudied. This research aimed to change this by estimating CVD incidence and mortality rates in Greenland from 1994 to 2021.
Methods: Using nationwide registers, a retrospective observational study was conducted, focusing on individuals born in Greenland to Greenlandic-born parents. Data was sourced from the Greenlandic Hospital Discharge Register and the nationwide electronic medical record.
Results: A total of 65,824 individuals were included, the age- and sex-specific incidence rates (IR) of ischemic heart disease (IHD), stroke, and heart failure (HF) declined from 1994 to 2021, with the most substantial decline observed for HF among women. Conversely, the IR of atrial fibrillation/flutter (AF/AFL) and myocardial infarction (MI) among men rose. The IR for stroke was particularly elevated compared to other CVD subgroups. Mortality rates for those diagnosed with CVD were 2.4 times higher than those without. Men exhibited a 40% elevated mortality risk relative to women.
Conclusion: The study provides pivotal insights into CVD trends within the Arctic Inuit population, highlighting both positive developments and areas of concern. Given the increasing elderly demographic in Greenland, proactive health strategies are crucial. Emphasizing primary prevention and addressing specific CVD risks, particularly the elevated stroke IR, is imperative for future public health efforts.

Introduction

Cardiovascular disease (CVD) is the leading cause of death globally, with ischemic heart disease (IHD) and stroke as the primary contributors (1). Through the second half of the 20th century, mortality from CVD has declined, especially in high-income Western countries, recent trends indicate a slowing in the decline, potentially driven by rising obesity and diabetes rates (2). The decrease in CVD-related deaths can be credited to improved, evidence-based treatment and a decline in risk factors (2,3). However, when it comes to the indigenous populations of the Arctic, comprehensive data on CVD is limited. Notably, there is a high prevalence of IHD and stroke among Canadian Inuit, and Alaskan natives (4,5).
Home to 56,609 inhabitants, Greenland is the world's largest island. The majority, 82%, are Inuit when defined as being born in Greenland to Greenland-born parents. Inuit in Greenland shares historical roots with Inuit populations in northern Canada, Alaska, and Siberia. From 1994 to 2021, there was a modest population increase from 55,419 to 56,421 in Greenland (6). Every year, nearly 10% of the population migrates to or from Greenland, primarily to or from Denmark (7). Over the past five decades, people have moved from the smaller settlements to the larger cities. Currently, approximately 60% of the population lives in the five major cities, Nuuk, Sisimiut, Ilulissat, Aasiaat, and Qaqortoq. Additionally, the number of elderly individuals (those above 50) has seen a significant increase from 1994 to 2021, rising from 7,440 to 15,666. Correspondingly, life expectancy has shown an upward trend from 1999 to 2021, with increases from 68.7 to 74.0 years for women and from 62.5 to 69.2 years for men (6).
Historically, the prevalence and nature of CVD in Greenland have been subject to different notions. In 1940,

Dr. Albert Berthelsen who worked in Greenland for several years, reported frequent cases of atherosclerosis among the Inuit (8). Contrarily, in the 1970s, Danish researchers, who examined the composition of the Inuit food, reported, that the incidence of myocardial infarction was low in Greenland (9–12). This perspective, however, was challenged by a comprehensive review in 2003, which concluded that the described low mortality rates were derived from unreliable data. They further concluded that stroke mortality probably were higher than in other populations (13). Concurring with this, a 2014 review concluded that coronary artery disease prevalence in Inuit populations is similar to other populations and the mortality of stroke is high (14). More recent studies further support the notion that IHD rates among Inuit mirror those in other Western societies (15–18). Furthermore, genetic analyses have identified genetic variants in the Greenlandic Inuit that increase the risk of diabetes, obesity, familial hypercholesterolemia, and CVD (19–21).

The traditional Inuit lifestyle has gradually been westernized over the past century. Consequently, Greenland has experienced a rise in obesity rates from 13% in 2003 to 27% in 2018, defined by a body mass index (BMI) exceeding 30 kg/m^2 (22). Conversely, the proportion of daily smokers has shown a decline from 68% in 1993 to 52% in 2018 (22). By 2021, 17,5% of those aged 20 and above were on antihypertensive medications (23). Factors such as smoking, alcohol consumption, poor diet, and physical inactivity amplify CVD risks, with research suggesting that an optimal lifestyle could prevent nearly 80% of IHD events (24–26). Clinical risk determinants for CVD include conditions like hypertension, dyslipidemia, diabetes, and obesity. Moreover, psychosocial factors, including depression, stress, and major life events, exhibit a significant correlation with IHD (27).

Given the data disparities, emerging risk factors, and lack of contemporary research on CVD incidence, this study aims to estimate the incidence and mortality of CVD in Greenland between 1994-2021, using data from the Greenlandic Hospital Discharge Register (GHDR) and the nationwide electronic medical record (EMR).

Materials and methods:

Design and setting:

We conducted a retrospective observational study using data from the GHDR and EMR databases in Greenland. In Greenland, health care is provided by healthcare clinics in the settlements, healthcare centers in the towns, hospitals in the larger towns, and the national hospital, Queen Ingrid's Hospital (QIH) in Nuuk. Discharge diagnoses on all patients admitted to hospitals or healthcare centers have since 1987 been registered in the GHDR. CVD diagnoses in the GHDR have been validated and are suitable for epidemiological use (28). The present EMR was implemented from 2013 to 2017, and all diagnoses given to patients admitted and in outpatient care are registered here. Diagnoses are recorded according to the International Classification of Disease 8th revision and 10th revision (29,30), and primary care diagnoses are recorded according to the International Classification of Primary Care (31).

Study population:

People born in Greenland to parents who were also born in Greenland, and who resided there between January 1st 1994 to December 31st, 2020, were included in the cohort. Entry date was the date of birth or date of migration to Greenland, exit date was the date of death and date of migration from Greenland or December 31st, 2020. Those who migrated from Greenland were excluded from the cohort at the time of migration but were reincluded if/when returning to Greenland. The time lived outside Greenland was censored. Patients diagnosed with CVD (*See Appendix*) in the GHDR or the EMR were identified and included as incident CVD. Data were linked using the unique Civil Registration Number.

Statistics:

All statistical calculations were made using the open-source software, RStudio (version 4.3.0). Before analysis, data was anonymized to ensure the privacy and security of the patient information. CVD diagnoses were divided into the subgroup categories; IHD and myocardial infarction (MI), stroke, heart failure (HF), and atrial fibrillation/flutter (AF/AFL) (*See Appendix*). When more than one diagnosis was recorded per individual in a CVD subgroup, only the earliest diagnosis was used. The date of CVD event was recorded as the date of diagnosis. Separate cohorts were established based on CVD subgroup and sex, and for each of these, a lexis object containing follow-up in multiple states and timelines was created (32). A new state (CVD) was created for those with a registered diagnosis, from the time of diagnosis. The lexis object was then split on the age timescale into 3-month periods. A Poisson regression model with the transition rate to the CVD state (incidence) as outcome and age and time (year) as predicted variables were made for each sex and CVD subgroup. Incidence rate (IR) per 100,000 person-years (PY) was predicted using the models for those aged 40, 50, 60, 70, and 80 years. Age at diagnosis was calculated as the median with interquartile range (IQR). Mortality rates of CVD were predicted by a similar model but based on the transition to death. The cohort included men and women in all CVD subgroups, again only the earliest diagnosis was used when more than one diagnosis was registered per individual. A Poisson regression model was made with the transition rate to death (mortality) as outcome and sex, age, time (year), and state (CVD or no CVD) as predicted variables. Hazard ratios comparing sexes and CVD statuses were derived from this model. For visualization, mortality rates per 1,000 person-years were predicted for men and women, with and without CVD, and between 30 and 90 years of age in 2010.

The total unadjusted crude incidence of the different CVD was predicted using a Poisson regression model with the transition to CVD as outcome and time (year) as the predictor variable.

For all models used, deviation from linearity was assessed by including the quadratic, cube, and common logarithm of the time variable in the Poisson regression model. When no deviation from linearity was found results were interpreted as linear, when deviation from linearity was found the time variable was splined into 14-year periods.

Ethics:

The study was approved by the Greenlandic Science Ethics Committee and the Greenlandic Healthcare Administration. It was conducted according to the Helsinki Declaration, all data from the EMR was anonymized and no informed consent from participants was needed.

Results:

A total of 65,824 people were included in the study. The mean follow-up time was 18.9 years, resulting in a total of 1,242,053.5 PY. The cohort-specific total risk time, mean follow-up time, events, and age at diagnosis are presented in Table 1.

Subgroup-specific incidence rates:

IHD and myocardial infarction:

The age- and sex-specific IR of IHD decreased from 1994 to 2021 for both men and women, stronger among women (figure 1). Men had higher IR at all ages. The IR increased with age, for both sexes. In 2021, the IHD IR, at 70 years of age was 1053.7 (CI: 855.7 – 1297.5) for men and 446.9 (CI: 337.6 – 591.6) for women, per 100,000 PY. The IR of myocardial infarction increased for men and decreased for women during the study period (figure 2). Men had the highest IR at all ages. The IR increased with age for men, among women the 70 years old had the highest IR. The IR at age 70, in 2021 was 397.9 (CI: 282.6 – 560.3) for men and 154.8 (CI: 93.9 – 255.0) for women, per 100,000 PY.

Stroke:
The age- and sex-specific IR of stroke decreased from 1994 to 2021 (figure 3). The decrease was more pronounced among women. Women had higher IR at ages 40, 50, and 80 years, the highest IR was among the 80 year old women. The IR increased with age, for both sexes. In 2021, the stroke IR, at 70 years of age was 1468.9 (CI: 1233.8 – 1748.8) for men and 1063.2 (CI: 876.6 – 1289.4) for women, per 100,000 PY.
Heart failure:
The age- and sex-specific IR of HF markedly decreased from 1994 to 2021 (figure 4). For women, the IR declined by a factor of 5 during the period. The IR for men decreased but was not as pronounced as for women. The highest IR was among the 80-year-old men and women. In 2021, the HF IR, at 70 years of age was 672.9 (CI: 536.7 – 843.6) for men and 258.9 (CI: 194.6 – 344.4) for women, per 100,000 PY.
Atrial fibrillation/flutter:
The age- and sex-specific IR of AF/AFL has increased among men and women (figure 5). The 80-year-old women had the highest IR, at all other ages, med had the highest IR. Men at 60 years of age had IR similar to that of the 70-year-old women. In 2021, the AF/AFL IR, at 70 years of age was 641.0 (CI: 480.4 – 855.4) for men and 495.5 (CI: 353.7 – 694.3) for women, per 100,000 PY.

CVD mortality
The total number of deaths was 11,623, of which 2941 were among people diagnosed with CVD. The median age at death was 66.5 (IQR: 52.3 – 76.1). People diagnosed with CVD had a mortality rate-ratio of 2.4. The total mortality rate ratio was 1.4 for men compared to women. The mortality rates per 1,000 PY, for men and women with and without CVD are presented in Figure 6.

The overall burden of CVD
As a measure of the absolute burden of CVD on the healthcare system given the demographic changes, unadjusted rates were calculated. The unadjusted incidence rate of stroke, IHD, and AF/AFL have increased during the period. Stroke had the highest unadjusted incidence rate. The unadjusted incidence rate of HF declined during the study period. The unadjusted CVD incidence rates, per 100,000 PY, across CVD subgroups are presented in Figure 7.

Discussion:
This is the first study to show the incidence rates of CVD in the Arctic Inuit. The study found that the age- and sex-specific IR of IHD, stroke, and HF have declined during the period from 1994 to 2021. The biggest decline was seen for HF among women. The IR of AF/AFL and MI among men increased. Those diagnosed with CVD had 2.4 the mortality of persons not diagnosed with CVD. The IR of stroke was high compared to the other CVD subgroups. The unadjusted IR of stroke, AF/AFL, and IHD increased, while HF decreased. The median age at first diagnosis was low across all subgroups.

The age-specific incidence rates
IHD and myocardial infarction:
The decreasing trend in the IR of IHD found in this study and the higher risk among men vs women in Greenland is comparable to that in most European countries (24). The declining IR, globally as in Greenland, can be explained by a raised focus on prevention, particularly declining rates of smoking, and improved treatment possibilities for clinical risk factors such as dyslipidemia, hypertension, and diabetes (22,23,33). The IR of IHD progressively increased with age for both men and women, however, the difference between the oldest groups (70 and 80 years old) is remarkably small. It can be hypothesized that older age groups may consist predominantly of ‘healthy survivors’ with individuals susceptible to IHD having already

succumbed to the disease in earlier age groups.
The age-specific IR across all age groups (40-80 years) found in 2021 is approximately 50% lower than the global estimates from the Global Burden of Disease (GBD) study 2019 (34). The low IR found in this study might reflect an actual lower incidence within the population. However, previous research has indicated that the incidence of IHD and associated markers are comparable to those in other Western populations (13,14,35). Furthermore, data show that the rate of revascularization in Greenlandic citizens is as high as in Danish citizens (18). A separate register study investigating the prevalence of AF in Greenland revealed that nearly half of the cases did not have a registered diagnosis of AF/AFL (36). Consequently, it is plausible to consider that the actual IR of IHD in Greenland may be higher than our findings suggest, potentially due to a significant number of undiagnosed cases.
MI was specifically categorized and further emphasized, as it is perceived as a more definitive diagnosis. Given the nature of the condition, MI is less likely to be overlooked and, therefore, underdiagnosed. As hypothesized, the IR of MI is more comparable to what is observed in the Danish population (37). This supports the theory, that other IHD diagnoses might be underestimated, possibly due to subtler presentation. The ascending trend in the IR of MI among men diverges from other populations, where the incidence has generally declined (24,34,37).
Stroke:
The IR of stroke found in this study is high, especially among the elderly. Compared to global estimates of stroke, the IR in Greenland is roughly 60% higher on average when comparing the 40 – 80 year old (34). The contribution from specific types of strokes, such as hemorrhagic and transient ischemic attacks, appears to be as expected and does not explain the high IR. Nevertheless, further investigation is needed, as some stroke diagnoses can be heterogeneous and might encompass various types of strokes.
According to our findings, the IR of stroke is noticeably higher than that of IHD in Greenland. This is contrary to what is commonly seen in other populations, where the IHD incidence is almost twice that of stroke (24,38). In Europe, the median age-standardized incidence estimates in 2019 were 293.3 for IHD and 135.5 for stroke (24). The explanation for the high IR of stroke is not obvious as IHD and stroke share risk factors (39). It could be that the prevalent risk factors in the Greenlandic population are more prone to cause stroke and less likely to result in IHD, different associations have been found between risk factors and CVD manifestations (40). It could also be hypothesized that the high stroke incidence could be caused by a genetic disposition, this could be due to the unique genetic background of the Greenlandic Inuit, resulting from years of isolation and descent from a small ancestral population (41).
The decreasing trend in the IR of stroke found in Greenland during the study period is consistent with what is seen in most European countries. According to the European Society of Cardiology (ESC), the median age-standardized incidence estimates of stroke declined from 190.2, in 1990 to 135.2 per 100,000 PY in 2019 (24). Similar decreasing trends are present for both the Global and Danish age-standardized IR of stroke according to the GBD study 2019 (34). The decline in IR could, like the decrease in IHD IR, be explained by better prevention and improved treatment possibilities of clinical risk factors for stroke.
Women had the highest IR among the youngest and the oldest, however, the IR decreased more among women than men during the study period, resulting in more comparable rates between the sexes by the end of the study in 2021. A similar difference in IR of stroke between the eldest men and women can be seen in the global estimated IR for stroke according to the GBD study 2019 (34). According to their data, the oldest women (85+ years) have the highest IR (34). Whether this is related to a real higher incidence among the older women or that older men have a higher competing risk leaving healthy survivors among the elderly, is unanswered.
HF:
We found a marked decline in HF IR in Greenland, especially among women. A decreasing incidence of HF is

seen in other populations, however not as noticeably (42). The IR of HF in Greenland seems to have declined from an alarmingly high level in the 1990s and early 2000s to a level more comparable to other populations. According to a Danish study including the entire adult Danish population from 1995 to 2012 the IR for those >74 years of age was about 120 per 10,000 PY in 2012 which is comparable to what we have found in the last part of the study period (43). Hence, it could be speculated that the high IR found in the early study period is somehow unreliable. Breathlessness, ankle swelling, and fatigue are the characteristic symptoms of HF, however, such symptoms could be caused by other disease than HF (44). The knowledge and diagnostic possibilities of HF have evolved since the ESC published its first guidelines for the diagnosis of HF in 1995 (45). The high IR early in the study could be caused by misinterpreting symptoms as caused by HF, combined with limited diagnostic possibilities, leading to overdiagnosis of HF. Oppositely, the decreasing incidence could be explained by an elevated focus on HF with reduced ejection fraction, hence overlooking HF with preserved ejection fraction, which is found to constitute nearly half of all HF (46). A reduction in rheumatic heart disease, which is known to cause HF, could also add to the decline in HF IR (47). Although not presented in this study due to a low absolute number of diagnoses we see a distinct decline in rheumatic heart disease during the study period. The drastic decline in HF IR could also be explained by improved health care in general including primary prevention, easier access to health care for assessment, and treatment of common HF causes like hypertension and IHD (44).

Atrial fibrillation/flutter:

The age-specific IR of AF/AFL increased during the study period, unlike what is seen globally and in Europe, where the IR has been stable (24,34). Compared to the global IR, the age-specific IR is comparable at study start and high by the end of the study (34). The IR of AF/AFL found in 2021 is roughly 85% higher compared to global estimates of 2019 (48). However, similar or lower when compared to what has been found in Denmark in 2018 (49). As AF/AFL can be paroxysmal, diagnosis can be difficult. It could be that the increasing incidence is due to better diagnostics as Holter monitoring devices are now more commonly used. Furthermore, AF/AFL risk factors include comorbidities such as hypertension, diabetes, HF, IHD, and obesity (50). Hence the increasing incidence of AF/AFL could be explained by an increase in the portion of people with these comorbidities. Globally AF/AFL is more common among men compared to women in all age groups (34). Corresponding to what we found except among the oldest where women had the highest IR.

The total burden of CVD in Greenland:

As life expectancy continues to increase, so does the proportion of elder people with a high incidence of CVD. Given the global increase in life expectancy, it may not appear surprising that crude CVD incidence rates are increasing worldwide (38). Since 1994, the population above 60 has doubled in Greenland (6). We found that the unadjusted incidence rate of IHD, MI, stroke, and AF/AFL increased as expected during the study period, with stroke being the most frequent. Surprisingly, the unadjusted incidence rate of HF showed a decline throughout the study period, aligning with the noticeable decrease in the age- and sex-specific IR of HF. The escalating incidence of CVD in Greenland, particularly among the elderly population, poses a significant challenge for the healthcare system in the future, and the high incidence rate of stroke is alarming and calls for public health efforts to understand the unique risk factors and health care needs in the Greenlandic population to effectively prevent and manage stroke.

As the proportion of older people with CVD continues to rise, so will the burden on healthcare resources. It is advisable to focus on primary prevention, involving the prevention of the development of modifiable risk factors. Tobacco smoking, overweight/obesity, dyslipidemia, hypertension, hyperglycemia, poor diet, and physical inactivity during childhood are all associated with early onset of atherosclerosis (51). The prevalence of obesity among preschool children was 21,7% in 2003 (52), and daily smoking is more

common than uncommon in Greenland (22). Therefore, a multifaceted effort from society is warranted, with a focus on health education, promoting access to healthy food, encouraging physical activity, and improving access to health care. Research and monitoring the prevalence of CVD, and CVD risk factors in Greenland is crucial for directing intervention strategies and evaluating their effect.

Mortality:

Individuals with CVD had more than twice the mortality of those without CVD, highlighting the health implications and potential risk of mortality associated with CVD. Interestingly, men had a 40% higher mortality risk compared to women, a trend comparable with observations in other populations (53). The differences in mortality found indicate a need for intensified CVD prevention, especially among men.

Strengths and Limitations:

This study utilized nationwide registers, which provides a robust representation of the Greenlandic population. Although nationwide and comprehensive, it includes the risk of missing data or underreporting. We hypothesize that underdiagnosis is prevalent in Greenland, yet it likely does not compromise the overall reliability of the observed incidence trends. Our study specifically focused on individuals born in Greenland to Greenlandic-born parents, thereby providing detailed insights into the incidence rates within this population. This approach is particularly relevant considering the significant annual migration into and out of Greenland. Given the limited number of healthcare professionals the possibility of coding errors or misclassifications, can be present based on errors among only a few individuals. Given the population size of Greenland, the number of incident cases is limited, hence a small change in cases per year can have a potentially big influence.

Conclusion:

This study presents insight into CVD trends among the arctic Inuit population, aligning largely with the observed trends in Western nations. Noteworthy are the elevated IR of stroke and the increasing IR of AF/AFL and MI in men, warranting further investigation. While the age-adjusted IR for most conditions is declining, the unadjusted rates show an increase driven by an aging population, signifying an increasing burden of CVD on the healthcare system. Highlighting the need for proactive preventive measures and initiatives to promote cardiovascular health within the community.
The nationwide registers used in this study provides a robust representation of the Greenlandic population. Given the healthcare challenges inherent in Greenland's remote and sparsely populated geography, it is plausible that the actual incidence of CVD may be higher than reported here. This is crucial for understanding CVD in Greenland and for guiding future public health strategies. Therefore, continued research and monitoring of CVD prevalence and risk factors in Greenland are essential to assess the health needs in this population.

Conflict of interest

The project was supported by Karen Elise Jensen's Foundation and the Novo Nordisk Foundation under grant number NNF20SA0064190. MEJ has received research grants from AstraZeneca, Sanofi Aventis, Boehringer Ingelheim and Novo Nordisk. MEJ holds shares in Novo Nordisk. FG has served as an advisor for Bayer, Pfizer, AstraZeneca, Ionis, Alnylam, Pharmacosmos, and Abbott. FG has received speaker's honoraria from Novartis and Orion Pharma. HEL received travel grants from A.P. Møller Foundation and Ketty and Ejvind Lyngsbæks Foundation.

Author contributions

HEL and MEJ conceptualized and designed the study and acquired the data. HEL conducted the statistical analysis, interpreted the data, and drafted the initial manuscript. UWG, FG, MLP and MEJ critically reviewed and revised the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Figures and Tables

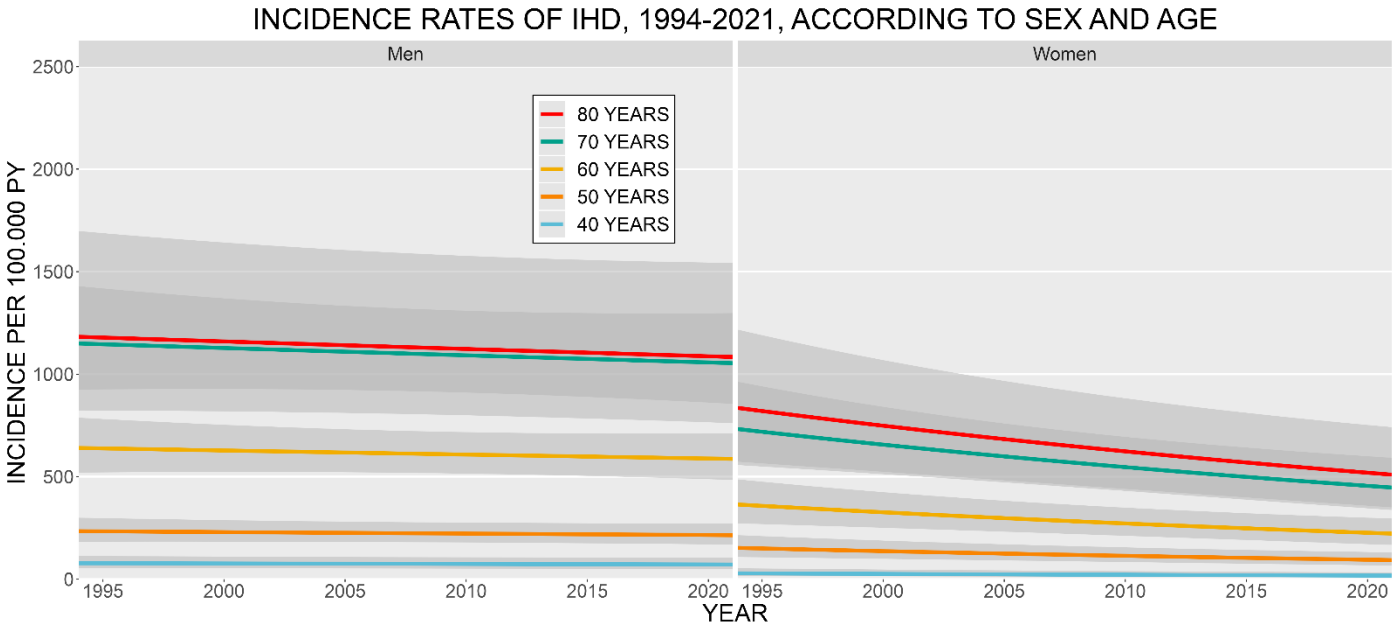


Figure 3. Incidence rate of ischemic heart disease (IHD) per 100,000 person-years between 1994 and 2021, according to sex at age 40, 50, 60, 70, and 80 years. The shaded area shows 95% confidence interval. PY = person-years.

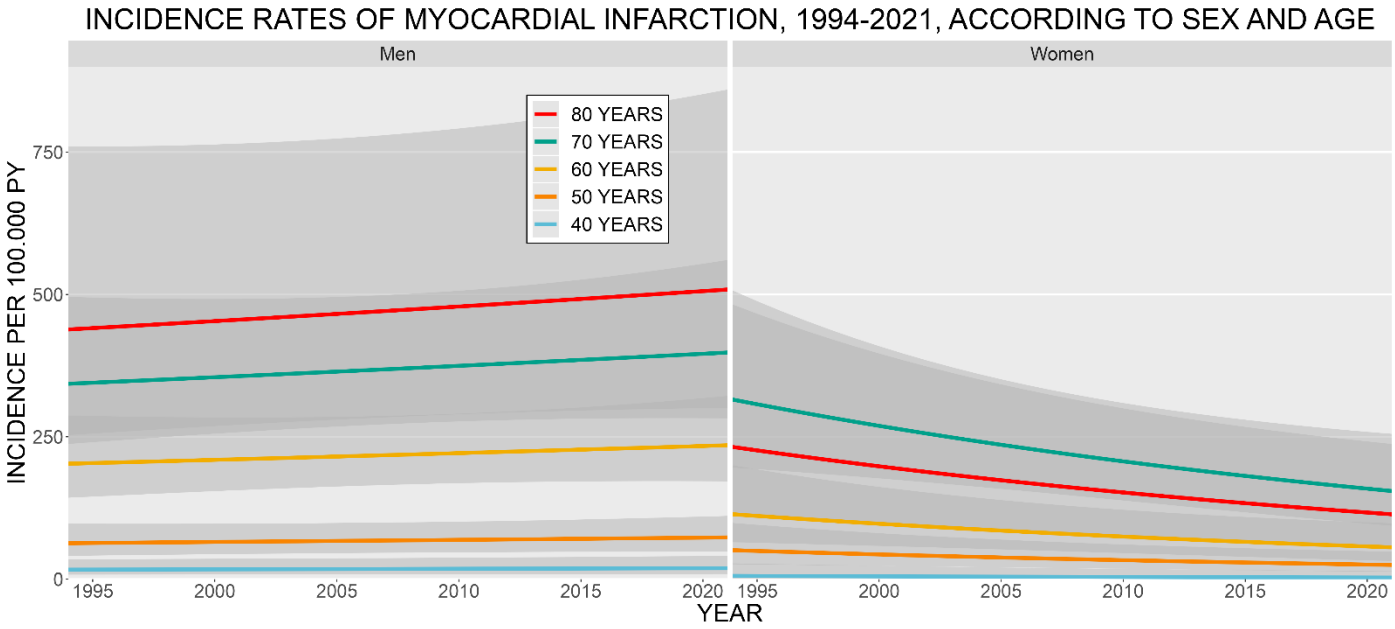


Figure 2. Incidence rate of myocardial infarction per 100,000 person-years between 1994 and 2021, according to sex at age 40, 50, 60, 70, and 80 years. The shaded area shows 95% confidence interval. PY = person-years.

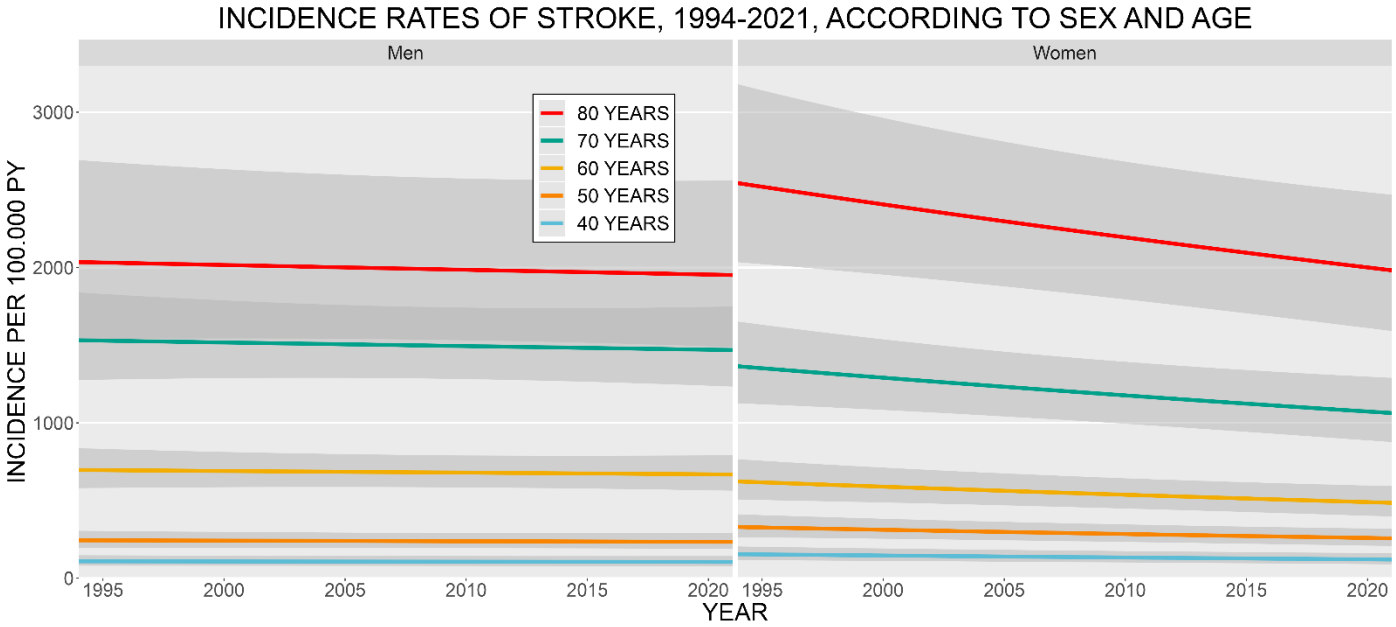


Figure 3. Incidence rate of stroke per 100,000 person-years between 1994 and 2021, according to sex at age 40, 50, 60, 70, and 80 years. The shaded area shows 95% confidence interval. PY = person-years.

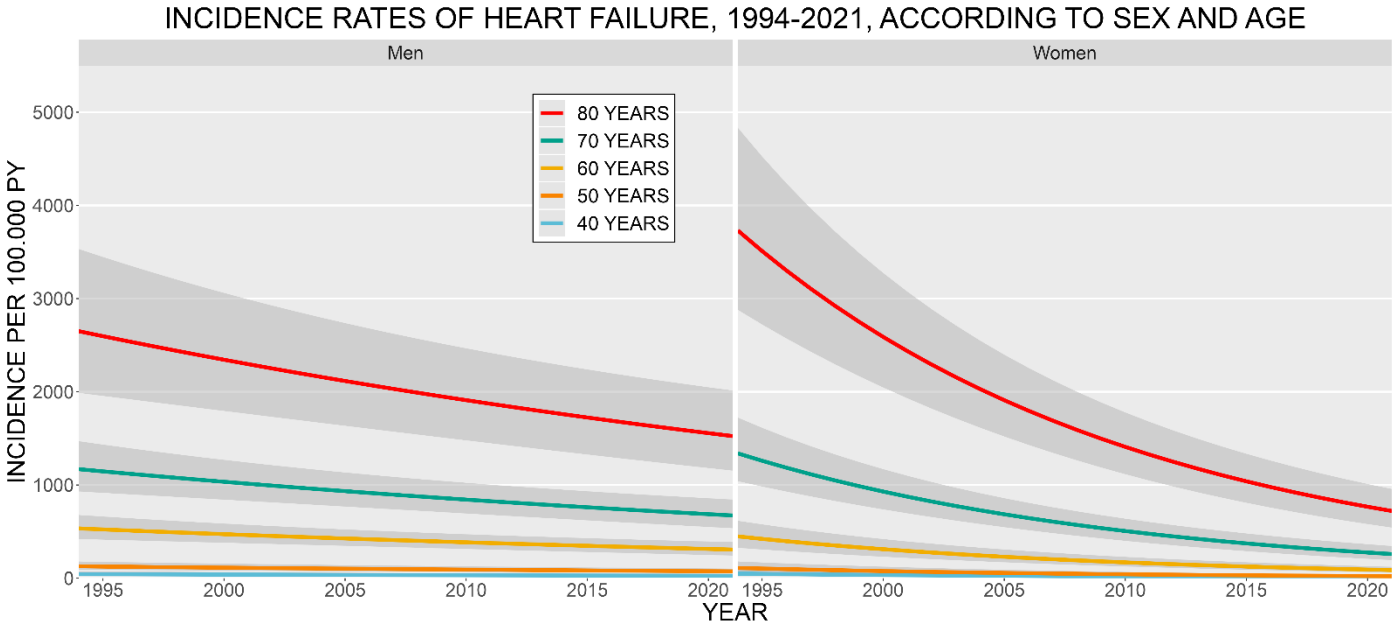


Figure 4. Incidence rate of heart failure (HF) per 100,000 person-years between 1994 and 2021, according to sex at age 40, 50, 60, 70, and 80 years. The shaded area shows 95% confidence interval. PY = person-years.

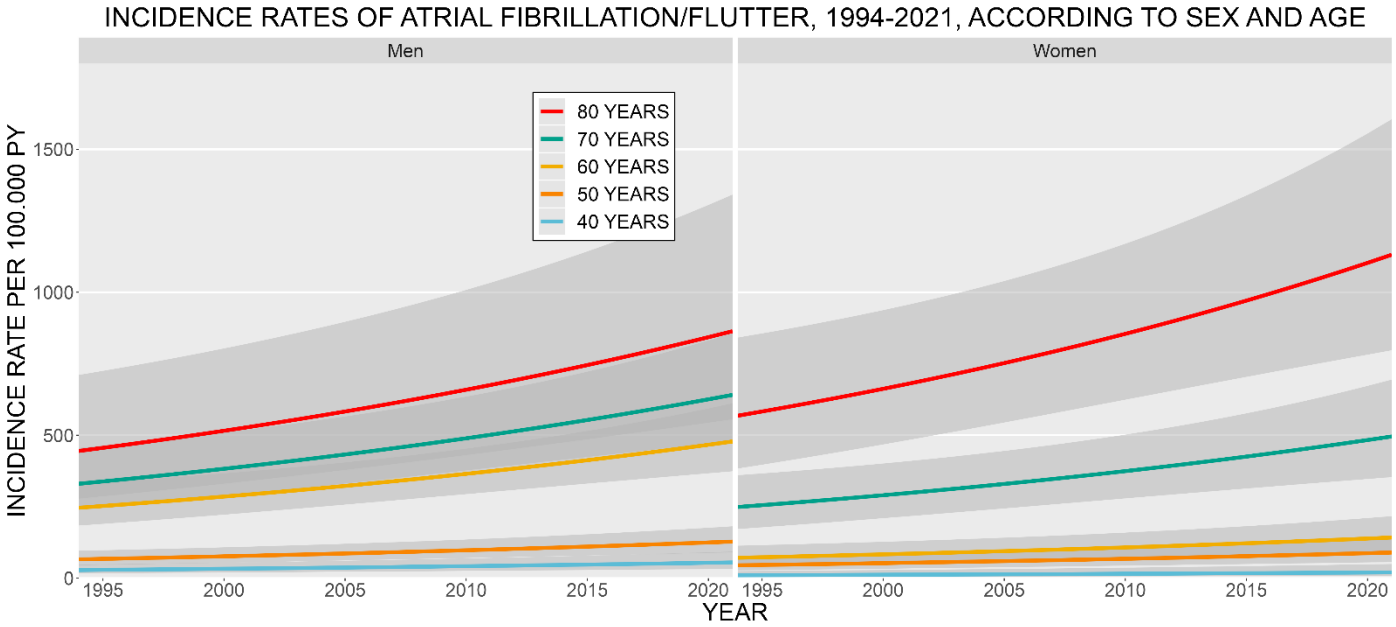


Figure 5. Incidence rate of atrial fibrillation/flutter per 100,000 person-years between 1994 and 2021, according to sex at age 40, 50, 60, 70, and 80 years. The shaded area shows 95% confidence interval. PY = person-years.

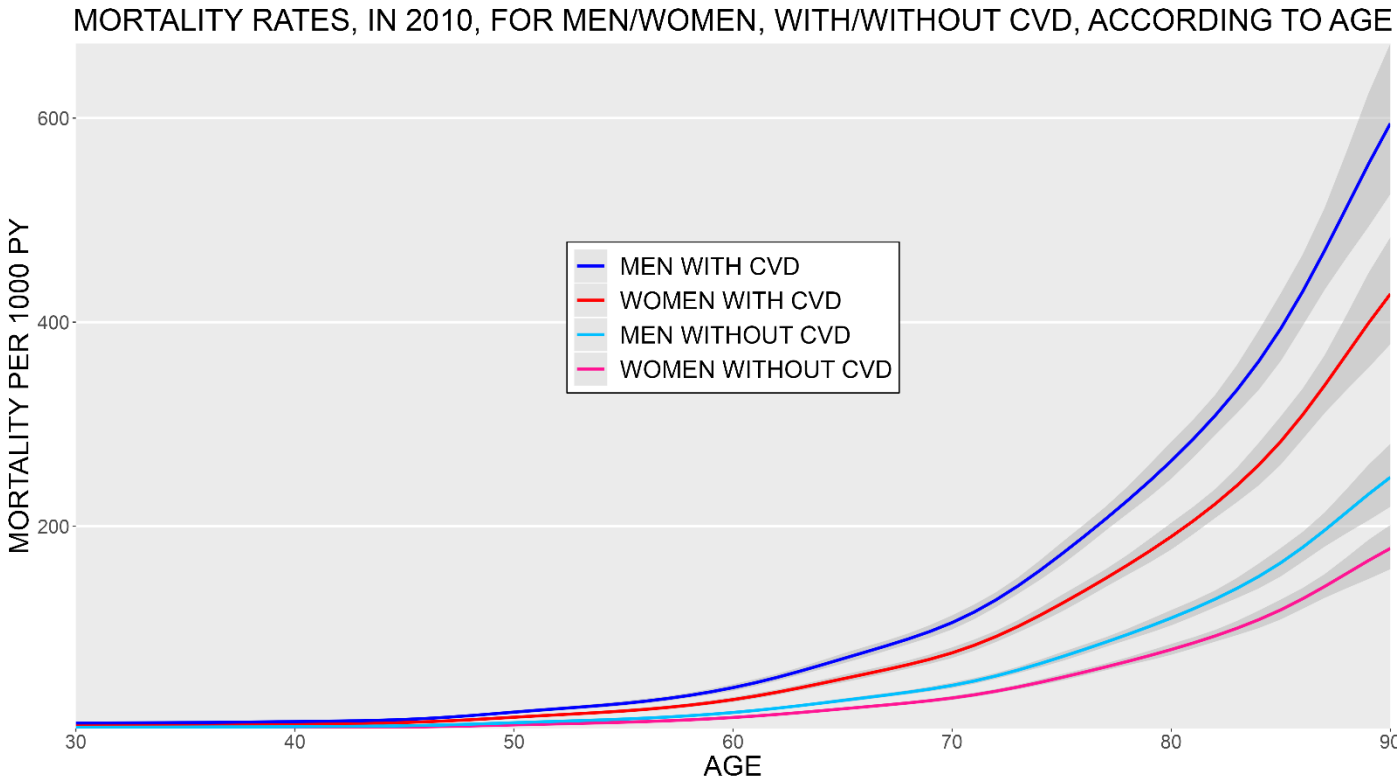


Figure 6. Mortality rate for men/women and with and without cardiovascular disease, based on mortality rates in 2010. The shaded area shows 95% confidence interval. Mortality rate ratio for cardiovascular disease: 2.4, and for Male sex: 1.4. PY = person-years, CVD = cardiovascular disease.

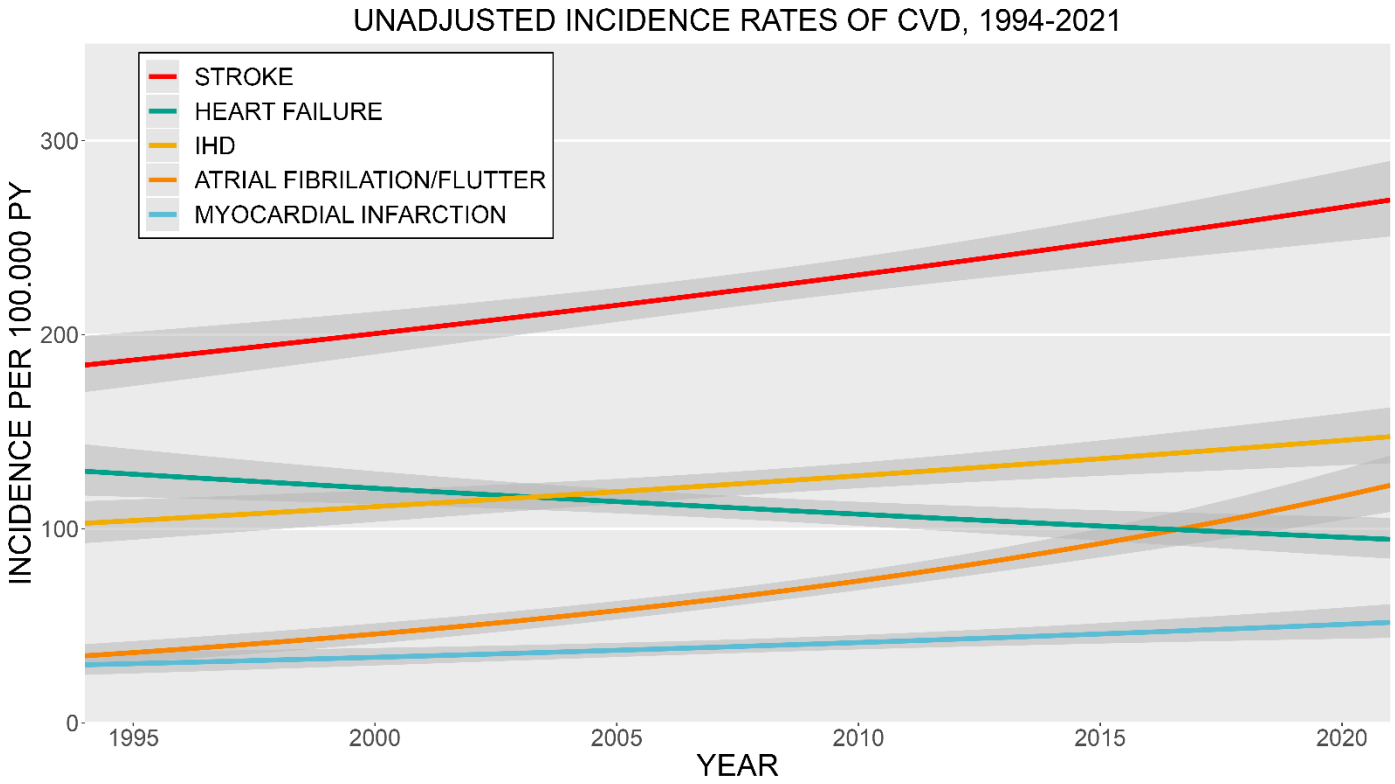


Figure 7. Unadjusted incidence rates of cardiovascular disease according to subgroup per 100,000 person years between 1994 and 2021. Shaded area shows 95% confidence interval. PY = person years, CVD = cardiovascular disease, IHD = ischemic heart disease.

IHD incidence rate	Men (n = 33434)	Women (n = 32352)
Total risk time (years)	626373.9	604452.3
Mean follow up time (years)	18.7	18.7
Events (n)	965	557
Age at diagnosis (years, median [IQR])	61.4 [53.6 – 69.1]	64.2 [55.2 – 72.1]

Myocardial infarction incidence rate	Men (n = 33451)	Women (n = 32364)
Total risk time (years)	631521.1	607639.3
Mean follow up time (years)	18.9	18.8
Events (n)	349	144
Age at diagnosis (years, median [IQR])	61.2 [53.5 – 69.0]	66.3 [57.5 – 72.4]

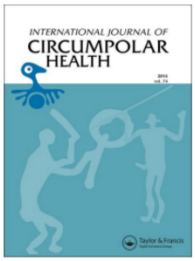
Stroke incidence rate	Men (n = 33384)	Women (n = 32300)
Total risk time (years)	623790.5	598996.4
Mean follow up time (years)	18.7	18.5
Events (n)	1412	1325
Age at diagnosis (years, median [IQR])	62.2 [53.6 – 69.5)	62.6 [51.1 – 73.1]

Heart failure incidence rate	Men (n = 33440)	Women (n = 32328)
Total risk time (years)	629955.7	605764.8
Mean follow up time (years)	18.8	18.7
Events (n)	802	573
Age at diagnosis (years, median [IQR])	66.8 [57.9 – 74.1]	70.9 [62.5 – 78.7)

Atrial fibrillation/flutter incidence rate	Men (n = 33444)	Women (n = 32353)
Total risk time (years)	630010.0	606281.2
Mean follow up time (years)	18.8	18.7
Events (n)	524	331
Age at diagnosis (years, median [IQR])	61.7 [54.0 – 69.8]	69.6 [60.7 – 77.1]
Mortality rate:	n = 65824	
Total risk time (years)	1242053.5	
Mean follow up time (years)	18.9	
Deaths (n)	11623	
Age at death (years, median [IQR])	66.5 [52.3 – 76.1]	

Table 1. Descriptive data according to cohort and gender. SD = standard deviation, IQR = interquartile range, n = number, IHD = ischemic heart disease.

Paper II:



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Prevalence and clinical features of heart failure in Greenland

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ABSTRACT

Heart Failure (HF) constitutes a significant burden for healthcare around the world. In Greenland, risk factors like smoking, diabetes, and obesity are prevalent. Yet, the prevalence of HF remains unexplored. This register-based cross-sectional study uses data from the national medical record in Greenland to estimate the age- and gender-specific prevalence of HF and to describe the characteristics of patients with HF in Greenland. A total of 507 patients (26% women) with a mean age of 65 years were included based on a diagnosis of HF. The overall prevalence was 1.1% and higher among men compared to women (1.6% vs. 0.6%, $p < 0.05$). The highest prevalence was among men above 84 years (11.1%). More than half (53%) had a body mass index above 30 kg/m2 and 43% were current daily smokers. The proportion diagnosed with ischaemic heart disease (IHD) was 33%. The overall prevalence of HF in Greenland is consistent with that in other high-income countries, yet high among men in some age groups, compared to Danish men. Almost half the patients were obese and/or smokers. A low prevalence of IHD was observed indicating that other factors may play a role in developing HF among Greenlanders.

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Heart failure; prevalence; epidemiology; Greenland; Arctic

Introduction

Heart failure (HF) is a clinical syndrome characterised by symptoms (such as breathlessness, fatigue, and often accompanied by fluid overload) caused by impaired heart function. HF is associated with high mortality rates, hospitalisation, and a negative impact on daily living [1]. Mortality from HF is similar to that of common cancer diseases, with survival rates of 80%, 50% and 25% after 1, 5 and 10 years, respectively [2–5]. HF was the third most common reason for hospitalisation in the USA in 2018 [6]. Furthermore, HF patients have impaired physical and social functioning and decreased quality of life [7].

The prevalence of HF in high-income countries is 1–2% and increases with higher age [8–10]. Approximately 5% of people above 75 years and 10% above 85 years have HF [9,11]. The lifetime risk of developing HF at age 55 is 30% [12]. HF risk factors include age, sex, hypertension, ischaemic heart disease (IHD), diabetes and obesity [13–15].

The prevalence of HF in the Greenlandic population is unknown but proposed to be high due to a high prevalence of risk factors such as hypertension, diabetes and obesity, and 52% of the Greenlandic population are regular smokers [16,17]. Moreover, the Greenlandic population is growing older, although the life expectancy is still remarkably lower compared to the Danish population [18,19].

This study aims to use data from the electronic medical record (EMR) to estimate the age- and sex-specific prevalence of HF in Greenland and to describe the characteristics of patients with HF in Greenland.

Methods

Design and setting

The study was performed as an observational cross-sectional study based on data extracted from the EMR used by the healthcare system in Greenland. Greenland is the largest island in the World. It covers more than 2 million square kilometres. The population of Greenland is 56,421, of which 82% are Inuit when defining Inuit as born in Greenland and both parents also born in Greenland [20]. One third of the population lives in the capital Nuuk; the remaining population lives in 16 minor towns and around 60 smaller settlements along the coast. The healthcare system in Greenland is publicly funded and all healthcare

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is delivered free of charge to all citizens in Greenland, including free medicine and dental care. The healthcare system is divided into five regions. Each region provides primary healthcare at a hospital in the largest town, healthcare centres in the remaining towns and healthcare clinics in the settlements. In addition to traditional outpatient primary care, some inpatient care, birth care, and minor surgical procedures are offered at regional hospitals and some healthcare centres. Specialised care is delivered by The National Hospital, Queen Ingrid's Hospital (QIH), in Nuuk or by a travelling specialist. Patients in need of highly specialised treatment are referred to treatment in Denmark.

All vital status information are registered in the national EMR, implemented from 2013 to 2017. Recorded data in the EMR is accessible nationwide; however, due to limited internet access, the Tasiilaq district in East Greenland is not sharing data with the remaining part of Greenland. All medications are prescribed electronically and are free of charge. All patients admitted to the department of internal medicine, Queen Ingrid Hospital, receive a diagnosis in the EMR. Diagnoses are recorded in the EMR according to the International Classification of Disease (ICD-10) [21], while primary care diagnoses are recorded according to the International Classification of Primary Care (ICPC-2) [22]. Patients suspected of HF are referred to the department of internal medicine, QIH, and examined in Nuuk or locally by a travelling cardiologist.

Study population

All patients registered with a diagnosis of HF (see Appendix, Table A1) in the EMR were included in the study and interpreted as HF patients. Information about age, sex, height, weight, systolic and diastolic blood pressure, left ventricular ejection fraction (LVEF), and smoking status was extracted from the EMR on all patients with HF included in the study. Only the most recent registered information was used. Body-mass index (BMI) was calculated based on weight and height. BMI was categorised as underweight (<18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2) and obese (≥ 30 kg/m^2). LVEF was categorised as heart failure with reduced ejection fraction (HFrEF) (≤40%), heart failure with mildly reduced ejection fraction (HFmrEF) (41–49%) and heart failure with preserved ejection fraction (HFpEF) (≥50%). Blood concentrations of thyroid-stimulating hormone (TSH), glycosylated haemoglobin (HbA1c), lipids (low-density lipoprotein (LDL), high-density lipoprotein (HDL), total cholesterol and triglycerides), creatinine, estimated glomerular filtration rate (eGFR), aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT) were included. Only the most recent test results were included. Information on diabetes and IHD was based on registered diagnosis (see Appendix 1) in the EMR. Examination for suspected IHD in Greenland includes a coronary computed tomography angiography (CCTA) which is only performed during admission to the department of internal medicine at QIH. For patients with a documented coronary disease on CCTA, a discharge diagnosis of IHD will be registered in the EMR.

Statistics

The prevalence of HF was calculated using 44,162 Greenlandic residents who were alive and aged 16 or above on the 1st of January 2022 [20]. A binomial generalised additive model with a diagnosis of HF as the response variable and age as the predictor variable was fitted for visualisation. Men and women were applied to this model separately. The continuous effect of age was assessed using a binomial generalised linear model with HF as the response variable and age as the predictor variable.

For comparison with data from other countries, patients were divided by sex and grouped into age groups. Prevalence with 95% confidence interval (CI) was determined for each of these groups. HF patients were grouped by sex and diagnosis of IHD for the presentation of characteristics. The probability distribution of continuous variables was assessed with a quantile-quantile plot. Mean and standard deviation (SD) were calculated for normally distributed continuous variables. Non-normally distributed continuous variables were presented as the median and interquartile range (IQR). Frequencies, categorical and continuous data were compared between sex and IHD groups using Fisher's exact test, Pearson's Chi-squared test, and Welch Two Sample t-test.

Results

A total of 507 patients were identified with a diagnosis of HF. Of those, three were excluded due to age below 16 years. Prevalence estimates grouped by sex and age are presented in Table 1. The overall prevalence of HF in Greenland was 1.1% [1.1–1.3], with a male preponderance (74%). The prevalence increased with age. The prevalence among men in the age groups 55–64 years, 65–74 years, and 75–84 years was 2.7% [2.3–3.2], 5.7% [4.8–6.8], and 9.3% [7.3–11.8], respectively. The highest prevalence was among older men, 11.1% [5.3–21.3] of men above 85 years of age had HF. Age as a continuous variable had a significant association with HF (Odds

Table 1. Distribution of heart failure according to age and gender. Data are frequency/% [95% confidence interval].

Age (years)	All patients	Female	Male
≥16	504/1.14% [1.05–1.25]	130/0.63% [0.53–0.75]	374/1.60% [1.44–1.77]
35–44	20/0.27% [0.17–0.42]	7/0.20% [0.09–0.43]	13/0.33% [0.18–0.58]
45–54	48/0.70% [0.53–0.94]	12/0.39% [0.21–0.70]	36/0.97% [0.69–1.35]
55–64	168/1.96% [1.68–2.29]	40/1.03% [0.75–1.42]	128/2.73% [2.29–3.24]
65–74	156/4.17% [3.56–4.88]	35/2.15% [1.52–3.01]	121/5.74% [4.80–6.84]
75–84	92/6.82% [5.56–8.34]	28/4.25% [2.89–6.16]	64/9.29% [7.28–11.77]
85+	13/6.74% [3.78–11.49]	5/4.13% [1.53–9.86]	8/11.11% [5.26–21.26]

ratio, 1.09; 95% CI, 1.08–1.09; $P < 0.001$). Figure 1 presents the prevalence of HF according to age and sex.

Characteristics

The mean age was 64.9 (standard deviation 12.8), with no difference between men and women. The overall percentage of daily smokers was 43% (men 44%, women 39%). More than half (53%) had a BMI of 30 kg/m^2 or above. A diagnosis of diabetes was present in 24% of the patients (men 24%, women 22%). A third was diagnosed with IHD (33%), more frequent among men than women (37% vs 23%, $P = 0.004$). Nearly half were diagnosed with HFrEF (49%), 24% with HFmrEF and 27% with HFpEF. The sex-specific characteristics of patients with HF are presented in Table 2.

Table 3 shows the characteristics of HF patients grouped by diagnosis of IHD. Of those diagnosed with IHD, 82% were men. Total cholesterol was lower among those diagnosed with IHD (no IHD 4.51 mmol/L, IHD 4.22 mmol/L, $P < 0.001$).

Discussion

The prevalence of diagnosed HF in Greenland in 2022, based on data from the EMR, was 1.1% and increased with age and male sex. The prevalence of obesity and smoking was high, and the prevalence of IHD was low.

Prevalence

The prevalence found is comparable to that in high-income countries of 1–2% [8–10]. This was lower than hypothesised based on the high prevalence of risk factors in Greenland. This may partly be explained by the fact that life expectancy in Greenland is ten years shorter than the average in high-income countries [18,19]. As life expectancy in Greenland is expected to rise, an increase in people with HF is anticipated

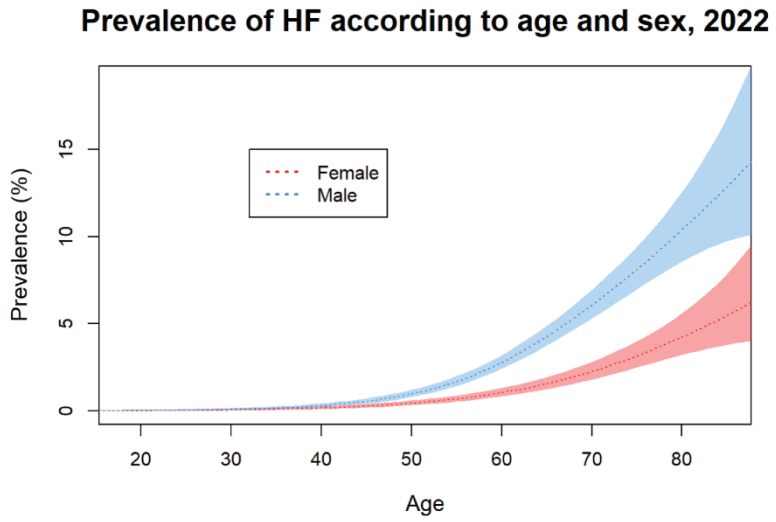

Figure 1. Estimated prevalence of HF in Greenland, 2022, based on registered ICD-2 code and ICPC-2 code for heart failure in the EMR. Shaded area shows 95% confidence interval.

Table 2. Characteristics according to gender. Data are frequency (%) unless stated otherwise.

Variable	Overall (n = 504)	Female (n = 130)	Male (n = 374)	p-value[1]
Age (years, mean (SD))	64.9 (11.4)	65.1 (12.8)	64.9 (11.0)	0.87
Smoking:				0.45
Yes	148 (43%)	34 (39%)	114 (44%)	
No	200 (57%)	53 (61%)	147 (56%)	
Missing	156	43	113	
Body Mass Index:				
Median [IQR; kg/m^2]	30.5 [26.2–35.1]	31.5 [27.2–36.2]	30.3 [26.0–34.6]	0.13
Missing	151	43	108	
Body Mass Index, class:				0.17
Underweight (<18.5 kg/m^2)	9 (2.5%)	4 (4.6%)	5 (1.9%)	
Normal (18.5–24.9 kg/m^2)	55 (16%)	10 (11%)	45 (17%)	
Overweight (25–29.9 kg/m^2)	101 (29%)	21 (24%)	80 (30%)	
Obese (≥30 kg/m^2)	188 (53%)	52 (60%)	136 (51%)	
Missing	151	43	108	
Systolic Blood Pressure:				
Mean (SD; mmHg)	129 (20)	126 (20)	130 (20)	**0.048**
Missing	49	10	39	
Diastolic Blood Pressure:				
Mean (SD; mmHg)	78.2 (11.9)	74.2 (11.0)	79.6 (12.0)	**<0.001**
Missing	49	10	39	
HbA1c:				
Mean (SD; mmol)	45.1 (10.5)	44.5 (9.6)	45.3 (10.8)	0.40
Missing	9	2	7	
LDL:				
Mean (SD; mmol/L)	2.62 (1.09)	2.75 (1.18)	2.58 (1.06)	0.15
Missing	14	2	12	
HDL:				
Median [IQR; mmol/L]	1.10 [0.90–1.40]	1.30 [1.00–1.60]	1.10 [0.83–1.30]	**<0.001**
Missing	14	2	12	
Total Cholesterol:				
Mean (SD; mmol/L)	4.41 (1.16)	4.74 (1.24)	4.30 (1.10)	**<0.001**
Missing	14	2	12	
TSH:				
Median [IQR; miu/L]	0.90 [0.56–1.51]	0.79 [0.51–1.34]	0.95 [0.60–1.59]	0.13
Missing	54	8	46	
Triglycerides, mmol/l				
Median [IQR; mmol/L]	1.70 [1.10–2.60]	1.80 [1.20–2.73]	1.70 [1.10–2.60]	0.11
Missing	14	2	12	
ASAT:				
Median [IQR; U/L]	28.0 [23.0–35.0]	26.0 [22.0–33.0]	29.0 [24.0–36.0]	0.27
Missing	44	5	39	
ALAT:				
Mean (SD, U/L)	45.5 (35.3)	37.6 (24.2)	48.3 (38.1)	**<0.001**
Missing	12	1	11	
Creatinine:				
Median [IQR; µmol/L]	87.0 [76.0–106.5]	78.5 [70.0–96.8]	90.0 [77.0–108.0]	**0.011**
Missing	1	0	1	
eGFR:				
Mean (SD; mL/min)	71.8 (27.4)	66.5 (39.5)	73.6 (21.6)	0.057
Missing	12	4	8	
LVEF:				
Mean (SD; %)	37.6 (12.2)	39.1 (13.6)	37.1 (11.7)	0.22
Missing	140	38	102	
Type of HF:				0.10
HFpEF	99 (27%)	33 (36%)	66 (24%)	
HFmrEF	43 (12%)	10 (11%)	33 (12%)	
HFrEF	222 (61%)	49 (53%)	173 (64%)	
Missing	140	38	102	
Diabetes	119 (24%)	28 (22%)	91 (24%)	0.52
Ischeamic Heart Disease	168 (33%)	30 (23%)	138 (37%)	**0.004**

n: Number of patients, SD: Standard deviation, IQR: Interquartile range.
[1]Pearson's Chi-squared test, Welch Two Sample t-test or Fisher's exact test.

[18]. The low prevalence may be related to underdiagnosing of chronic disease in Greenland. Recent studies have found, e.g. a low prevalence in the treatment of osteoporosis in Greenland and diagnosis of psoriasis in Nuuk, speculating that the real prevalence is higher [23,24]. If diagnosed before the introduction of the existing EMR (2013–2017), diagnosis registration would require registration in the new EMR. Patients with fewer symptoms could be missing diagnosis if not having recent contact with

Table 3. Characteristics according to IHD-diagnosis. Data are frequency (%) unless stated otherwise.

Variable	Overall[1] (n = 504)	No IHD (n = 336)	IHD (n = 168)	p-value[1]
Gender:				**0.004**
Female	130 (26%)	100 (30%)	30 (18%)	
Male	374 (74%)	236 (70%)	138 (82%)	
Age (years, mean (SD))	64.9 (11.4)	64.4 (12.2)	66.0 (9.7)	0.12
Smoking:				0.087
Yes	148 (43%)	102 (46%)	46 (37%)	
No	200 (57%)	120 (54%)	80 (63%)	
Missing	156	114	42	
Body Mass Index:				
Median [IQR; kg/m^2]	30.5 [26.2–35.1]	30.9 [25.9–35.9]	30.4 [26.6–34.2]	0.070
Missing	151	115	36	
Body Mass Index, class:				0.057
Underweight (<18.5 kg/m^2)	9 (2.5%)	9 (4.1%)	0 (0%)	
Normal (18.5–24.9 kg/m^2)	55 (16%)	32 (14%)	23 (17%)	
Overweight (25–29.9 kg/m^2)	101 (29%)	59 (27%)	42 (32%)	
Obese (≥30 kg/m^2)	188 (53%)	121 (55%)	67 (51%)	
Missing	151	115	36	
Systolic Blood Pressure:				
Mean (SD; mmHg)	129 (20)	129 (20)	128 (19)	0.58
Missing	49	39	10	
Diastolic Blood Pressure:				
Mean (SD; mmHg)	78.2 (11.9)	78.2 (12.0)	78.1 (11.9)	0.94
Missing	49	39	10	
HbA1c:				
Mean (SD; mmol/mol)	45.1 (10.5)	44.4 (9.7)	46.4 (11.9)	0.062
Missing	9	8	1	
LDL:				
Mean (SD; mmol/L)	2.62 (1.09)	2.65 (1.11)	2.58 (1.06)	0.55
Missing	14	11	3	
HDL:				
Median [IQR; mmol/L]	1.10 [0.90–1.40]	1.20 [0.90–1.40]	1.10 [0.90–1.40]	0.12
Missing	14	11	3	
Total Cholesterol:				
Mean (SD; mmol/L)	4.41 (1.16)	4.51 (1.18)	4.22 (1.10)	**0.006**
Missing	14	11	3	
TSH:				
Median [IQR; miu/L]	0.90 [0.56–1.51]	0.91 [0.57–1.51]	0.90 [0.56–1.50]	0.30
Missing	54	37	17	
Triglycerides, mmol/l				
Median [IQR; mmol/L]	1.70 [1.10–2.60]	1.80 [1.10–2.60]	1.70 [1.10–2.60]	0.45
Missing	14	11	3	
ASAT:				
Median [IQR; U/L]	28.0 [23.0–35.0]	28.0 [23.0–37.0]	28.0 [23.0–33.0]	**0.045**
Missing	44	33	11	
ALAT:				
Mean (SD, U/L)	45.5 (35.3)	46.2 (39.2)	44.2 (25.9)	0.50
Missing	12	9	3	
Creatinine:				
Median [IQR; µmol/L]	87.0 [76.0–106.5]	88.0 [76.0–104.5]	87.0 [75.8–110.0]	0.42
Missing	1	1	0	
eGFR:				
Mean (SD; mL/min)	71.8 (27.4)	72.7 (30.1)	70.1 (21.1)	0.27
Missing	12	8	4	
LVEF:				
Mean (SD; %)	37.6 (12.2)	37.6 (13.0)	37.6 (10.6)	0.99
Missing	140	99	41	
Type of HF				0.63
HFpEF	99 (27%)	68 (29%)	31 (24%)	
HFmrEF	87 (24%)	57 (24%)	30 (24%)	
HFrEF	178 (49%)	112 (47%)	66 (52%)	
Missing data	140	99	41	
Diabetes	119 (24%)	73 (22%)	46 (27%)	0.16

n: Number of patients, SD: Standard deviation, IQR: Interquartile range.
[1]Pearson's Chi-squared test, Welch Two Sample t-test or Fisher's exact test.

the healthcare system. One interesting finding is a high age-grouped prevalence. Compared to the Danish population, the prevalence of HF was approximately 25% higher among men and women in some age groups. The most significant difference was among men aged 65–74 years (5.74% vs 4.30%) and women aged 55–64 years (1.03% vs 0.77%) when compared to the prevalence in 2018 from the

Danish Heart Foundation [25]. A Danish nationwide register study of chronic disease found a prevalence of HF among those aged 45–74 years of 0.95% [26]. We found the prevalence in the same age group in Greenland was markedly higher (2.63% [2.35–2.92%]).

Estimated HF prevalence among indigenous people are sparse, but in 2015 Atzema et al. found the prevalence of congestive heart failure, among 12,550 Métis persons, above the age of 20 and living in Ontario, Canada, was 5.14% [27]. And according to the Public Health Agency of Canada the prevalence of HF in Nunavut is 6.4% among those aged 40 and older [28]. In these age groups we found the prevalence to be 1.22% and 2.04% respectively. The populations have limited access to healthcare due to geographical similarities and other sociodemographic challenges, which may explain the higher prevalence. However, HF may be more common among Inuit and genetically related indigenous people than other western populations.

Characteristics

The average Greenlandic patient with HF is ten years younger compared to what has been found in other HF populations. A Swedish register study, including 36,420 people diagnosed with HF in 2010, found a mean age of 77 years (women 80 years, men 74 years) [8]. Another study, including 93,074 patients diagnosed with HF from 2002 to 2014 in the UK (UK), found a mean age of 77 years (women 79 years, men 74 years) [10]. The early onset of HF among the Greenlandic population may contribute to the difference in life expectancy.

The frequency of daily smokers was high (43%) compared to the HF population in the UK, where 13% were smokers [10]. The high frequency of smokers was expected as the population survey in Greenland in 2018 found a prevalence of 52% daily smokers [16].

Obesity (BMI>30) was common among Greenlandic HF patients (53%). The 2018 population survey found that 27% of the Greenlandic population were obese [16] and 32% of the HF population in the UK [10]. Suggesting that obesity among Greenlandic Inuit induce HF through pathologic pathways such as insulin resistance, inflammation of adipokines and cardiac lipotoxicity as well as increased predisposition to established risk factors for HF [29,30].

The proportion of HFpEF and HFmEF was high compared to that reported from Europe [31]. Whether this relates to the high proportion of patients with obesity and diabetes, or other factors remains to be elucidated.

The proportion diagnosed with diabetes was similar to that in the HF populations in Sweden and the UK, where around one quarter of the population have diabetes [8,10]. This is consistent with the knowledge of diabetes increasing the incidence of HF [32].

The proportion diagnosed with IHD was low compared to that in other HF populations, where around half had IHD [8,10]. Furthermore, studies suggest that the incidence of IHD in Greenland is higher than earlier anticipated. The prevalence of markers for IHD based on self-reported myocardial infarction (MI), angina pectoris and ischaemic changes in electrocardiogram among 1316 Inuit in Greenland was comparable to that in Western populations [33]. A retrospective register study of reported mortality causes found a similar or slightly lower incidence of IHD in Greenland compared to that in Denmark from 1965 to 1998 and concludes that the evidence for low mortality of IHD among Inuit is based on unreliable mortality statistics [34]. The low prevalence of IHD found in this study may be influenced by underdiagnosis due to vast distances and lack of local specialised staff and diagnostic equipment. It could also be hypothesised that the aetiology of HF among the Greenlandic people is different from that in other countries. The Inuit in Greenland may be more likely to develop HF through non-ischaemic pathways caused by obesity and/or diabetes. Whether this could be explained by genetics is unknown, but the Greenlandic founder population has historically been isolated, resulting in sparse genetic diversity but high allele frequencies. Recently Inuit-specific genetic variants associated with diabetes, obesity, and familial hypercholesterolaemia with large effect sizes have been identified [35–37]. It could be suggested that a genetic disposition for non-ischaemic HF is prevalent in this population but requires further studies.

Strengths and limitations

This study is the first to describe the age- and sex-specific prevalence of HF in Greenland. Furthermore, around 90% of the entire population in Greenland was included in the study. Also, the study was based on standardised non-biased data drawn from the nationwide EMR. The prevalence estimated in this study is the prevalence of diagnosed HF, while the actual HF prevalence may be higher. The low prevalence of IHD may be influenced by underdiagnosis. However, patients diagnosed with HF are referred to CCTA. Patients suffering from HF may be misdiagnosed outside of Nuuk because of limited diagnostic possibilities. Information on hypertension and other relevant comorbidities, as well as treatment was not included in the study.

Conclusion

We found the prevalence of HF in Greenland was 1.1% which is consistent with that in high-income countries.

The age-grouped prevalence among those aged 45–74 years was high compared to that of the Danish population. The prevalence of HF patients without IHD was high. Despite the presence of risk factors, unknown risk factors including genetics, should be explored.

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Appendix

Table A1. List of ICD-10 and ICPC-2 codes.

Heart failure:	
ICD-2 codes:	
I11.0:	Hypertensive heart disease with heart failure.
I13.0:	Hypertensive heart and chronic kidney disease with heart failure and stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease.
I13.2:	Hypertensive heart and chronic kidney disease with heart failure and with stage 5 chronic kidney disease, or end-stage renal disease.
I42.0:	Dilated cardiomyopathy.
I42.6:	Alcoholic cardiomyopathy.
I42.7:	Cardiomyopathy due to drug and external agent.
I42.9:	Cardiomyopathy, unspecified.
I50.0-I50.9:	Heart failure.
ICPC-2 codes:	
K77:	Heart failure.
Diabetes:	
ICD-10 codes:	
E10:	Type 1 diabetes mellitus.
E11:	Type 2 diabetes mellitus.
E12:	Malnutrition-related diabetes mellitus.
E13:	Other specified diabetes mellitus.
E14:	Unspecified diabetes mellitus.
ICPC-2 codes:	
T89:	Diabetes insulin dependent.
T90:	Diabetes non-insulin dependent.
Hypertension:	
ICD-10 codes:	
I10:	Essential Hypertension.
I11:	Hypertensive heart disease.
I12:	Hypertensive Chronic Kidney Disease.
I13:	Hypertensive heart and chronic kidney disease.
I15:	Secondary Hypertension.
ICPC-2 codes:	
K85:	Elevated blood pressure.
K86:	Hypertension uncomplicated.
K87:	Hypertension complicated.
Ischaemic heart disease (IHD):	
ICD-10 codes:	
I20:	Angina pectoris.
I21:	Acute myocardial infarction.
I22:	Subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction.
I23:	Certain current complications following ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction (within the 28 day period).
I24:	Other acute ischaemic heart disease.
I25:	Chronic Ischaemic heart disease.
ICPC-2 codes:	
K74:	Ischaemic heart disease with angina.
K75:	Acute myocardial infarction.
K76:	Ischaemic heart disease without angina.

Paper III:

Genetic screening of Dilated Cardiomyopathy variants among Greenlanders.

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Abstract:

Background: This study investigates the genetics of dilated cardiomyopathy (DCM) in Greenlanders, a population genetical distinct due to historical isolation. We focused on Greenlandic heart failure (HF) patients without ischemic heart disease (IHD).

Methods: Whole-genome sequencing was performed on 58 Greenlandic HF patients, specifically targeting known DCM genes. Selection criteria included an ejection fraction below 40%, age under 60, and no history of IHD, arrhythmia, or valve disease. We focused on known DCM genes to identify potential pathogenic variants.

Results: Of 44 genes associated with DCM the study identified one likely pathogenic variant (p.K637E in MYH7) present in 3% of the cohort. This contrasts with higher pathogenic variant rates in other DCM studies.

Conclusion: The findings emphasize the distinct genetic landscape of DCM in Greenlanders. The low prevalence of pathogenic variants suggests a combination of genetic and environmental factors in DCM pathogenesis and highlights the need for genetic discovery studies in diverse populations like the Greenlandic to understand the genetic causes for DCM.

Introduction

Heart failure (HF) is a syndrome caused by impaired function of the heart. It affects approximately 2% of the adult population worldwide and is responsible for considerable morbidity and mortality (1). The etiology of HF is not singular but encompasses a broad range of conditions affecting the heart (2,3). Among the common causes is cardiomyopathy with dilated cardiomyopathy (DCM) being the most prevalent (4). DCM is characterized by an enlarged left ventricle and reduced contractility, leading to systolic dysfunction, in absence of abnormal loading conditions or ischemic heart disease (IHD) (4,5). Both environmental and genetic factors are involved in the pathogenesis of DCM with about one in four DCM patients having a monogenic cause (6,7). Pharmacological treatment has been shown to decrease mortality, reduce hospitalizations, and improve quality of life for the patient (4,8). Early identification of those at increased risk is beneficial to optimize treatment strategies and reduce associated risks (9). However, diagnosing HF is challenging, as its symptoms often resemble those of other conditions, especially in in the elderly who typically have comorbidities (10). Genetic testing is a valuable tool in identifying individuals at high risk of developing DCM. However, for such testing to be most effective, a thorough understanding of the genetic predisposition is crucial.

The Greenlandic population have a unique genetic composition due to the ancestral demographics of Greenland. The Thule people, who settled in Greenland around 1200 BC, are the direct ancestors of the contemporary Greenlandic Inuit (11). Genetic research indicates that the ancestral Greenlandic population has been historically isolated and originated from a small founder population (12). This has led to reduced genetic diversity, wherein the frequency of rare disease-associated genetic variants can become amplified. Furthermore, the proportion of HF patients diagnosed with IHD is lower in Greenland compared to other HF cohorts, suggesting the presence of alternative pathological pathways (13). Genetic studies including the Greenlandic population have led to the discovery of novel variants associated with diabetes and obesity (14–17). Furthermore, certain genetic variants, rare in other populations can be more prevalent among Greenlanders. For instance, a low-density lipoprotein (LDL) receptor variant (p.G137S) associated with increased LDL cholesterol levels is estimated to be present in nearly 29.5% of the population (18). An LDL receptor variant that is otherwise estimated as extremely rare in non-Arctic populations (18).

Encouraged by the potential benefits for future treatment of DCM in Greenland and the unique genetic composition of Greenlanders, we performed whole-genome sequencing on 58 Greenlanders with HF with reduced ejection fraction and absence of apparent causes like IHD. We screened the known genes associated with dilated cardiomyopathy (DCM) among these phenotypes.

Methods

Design:
A clinical cross-sectional study, screening HF patients for known and novel variants in genes known to be associated with DCM.

Setting:
Greenland is the world's largest island and covers more than 2 million square kilometers. The population is estimated to just over 56,000 people of which one third live in the capital Nuuk. The rest of the population lives in 16 minor towns and 60 smaller settlements along the coast. Health care is delivered free of charge to all citizens in Greenland including free medicine and dental care. The health care system in Greenland is divided into 5 regions. Each region has one regional hospital in the region's largest town, while healthcare centers and smaller healthcare clinics deliver care in towns and settlements respectively.

Study participants:
All patients diagnosed with HF (ICD-10: I50-50.9) in the electronic medical record (EMR) were assessed for eligibility. All who met inclusion and exclusion criteria were invited to participate in the study.

Inclusion criteria:

- Registered ICD-10 code for HF in the EMR (ICD-10 code: I50-50.9).
- Age 60 or under, at time of diagnosis.
- Left ventricular ejection fraction (LVEF) of 40% or less, based on echocardiography at time of diagnosis.
- Informed consent.

Exclusion criteria:

- History of IHD based on registered ICD-10 code in the EMR (ICD-10 code: I20.0-25.9), coronary computed tomography angiography (CCTA) with significant stenosis or IHD detected by invasive coronary angiography.
- Primary heart valve disease or aortic stenosis based on echocardiography.
- Atrial fibrillation prior to HF, based on registered ICD-10 code in the EMR (ICD-10 code: I48).
- Structural congenital heart disease based on registered ICD-10 code in the EMR (ICD-10 code: Q20-28) and self-report.
- Previous treatment with chemotherapy based on self-report.
- Diagnosed with endocarditis based on ICD-10 code in the EMR (ICD-10 code: I33.0-33.9).

Measures:
All patients were invited to a local healthcare facility where examination and blood sampling were conducted by healthcare professionals. Examination included height, weight, blood pressure, and electrocardiogram (ECG), examinations were done according to standardized procedure. Blood samples were drawn and analyzed for pro-brain natriuretic peptide (pro-BNP), total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, glycated hemoglobin (HbA1c) and estimated glomerular filtration rate (eGFR), creatinine, hemoglobin. Urine samples were obtained for analysis of urine albumin-creatinine ratio. Blood samples, for whole genome sequencing, were transported to Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.

DNA extraction
Genomic DNA was extracted from blood buffy coat by salt precipitation. DNA integrity and quantity was checked using Agilent TapeStation (Agilent Technologies, Santa Clara, California, USA) and Qubit (ThermoFisher, Waltham, Massachusetts, United States).

Whole genome sequencing and variant calling
Whole genome sequencing (WGS) and variant calling has been described in detail previously (19). Briefly, MGI DNBSEQ-T7 with DNBSEQ-T7RSHigh-Troughput Sequencing Kit Model FCL PE150 (MGI, Shenzhen, China) was used for WGS. Read processing, mapping, genotyping, and annotation was performed as described in Gul et al. 2023 (19), using a modified version of the PALEOMIX pipeline (20) available at https://github.com/Hansen-Group/NGSPipeline. Briefly, QC was performed using FastQC v0.12.1 (https://www.bioinformatics.babraham.ac.uk/projects/fastqc/) and MultiQC v1.14 (21), read processing was performed using fastp v0.23.4 (22), read mapping to the hg38 human reference genome from the GATK resource bundle was performed using bwa-mem2 v2.2.1 (23), post-processing was performed using samtools v1.18 (24), and base score recalibration, haplotyping, genotyping, and variant recalibration was performed using GATK v4.4.0.0. (25). The resulting VCFs were annotated using VEP v104 (26) using a custom pipeline available at https://github.com/cbmrphenomics/annovep.

Genetic Screening:
About 100 genes have been found to be related to DCM. The Clinical Genome Resource (ClinGen) have classified the genes by disease-specific metrics (27), resulting in 19 genes classified as having definitive, strong, or moderate evidence (DSME), and 25 genes classified with limited evidence (27). These 44 genes were selected for the genetic screening.

Variant screening
The annotated WGS data was filtered for the 44 genes. Variants with a moderate or high calculated variant consequence were retained, while variants with low, modifier, or missing consequence were excluded. Variants found in dbSNP were considered known. For variants reviewed in ClinVar without conflicts, the ClinVar interpretation was used as the classification, otherwise manual classification was performed according to American College of Medical Genetics criteria (28).

Ethics:
The study was approved by the Science Ethics Committee in Greenland and was conducted in accordance with the declaration of Helsinki. All participants gave written informed consent.

Results

A total of 545 persons were diagnosed with HF in the EMR, of these 75 met the inclusion and exclusion criteria and were invited to participate in the study. Out of those invited, 17 were unable to participate due to relocation, illness, voluntary non-participation, or lack of response, resulting in a final cohort of 58 individuals. The recruitment flow is illustrated in figure 1.

Clinical characteristics:
Of the 58 patients included, 61% were men (n = 36). The mean age at the time of HF diagnosis was 48.1 years (SD: 10.2). Participants resided throughout Greenland with no obvious skewed geographic overrepresentation when the study was conducted. Characteristics are presented in table 1.

Genetic investigation:
A total of 4,234 variants were found within 19 genes with DSME of association with DCM (figure 1A) and a further 13,016 variants were found within 25 genes with limited evidence of association with DCM (figure 1B). After filtering for moderate or high predicted functional impact and global minor allele frequency <5%, 58 potentially functional variants remained in the genes with DSME, and 52 variants remained in genes with limited evidence.

The individual characteristics of the identified genetic variants are summarized in table 1 and 2. The majority of variants were known. Six variants in DCM-associated genes with DSME of association, and four variants in DCM-associated genes with limited evidence of association were not found in the dbSNP database. The majority of variants (32 variants in genes with at least moderate evidence of association and 38 variants in genes with limited evidence) were classified as benign or likely benign (B/LB), either in ClinVar or manually classified, while a further 25 and 14 variants were classified as variants of unknown significance (VUS). A single variant, identified in two related individuals, in *MYH7* (a gene with definitive evidence of association with DCM) p.K637E was classified as likely pathogenic.

Given two carriers of a likely pathogenic variant, the total positive prevalence within this cohort was 3%.

Discussion

In this study, we analyzed the genomes of 58 Greenlandic individuals with DCM, focusing on identifying genetic causes of DCM in Greenland. Notably, we found that only a small proportion (3%) of these individuals carried pathogenic or likely pathogenic variants. This finding is in sharp contrast with other heart failure cohorts which generally have a higher proportion of positive genetic findings. A Danish cohort of 31 patients with idiopathic DCM found that 26% of patients were carriers of disease-associated variants (29). An American study found a positive result in 17% of unrelated adult and pediatric DCM cases (30). A study assessing the impact of gene panel size on the test yield found that a 46-gene panel found clinically relevant

genetic variations in 37% of patients, compared to 10% using a 5-gene panel (31). A Dutch study of 689 DCM patients found that 19% of patients were carriers of pathogenic or likely pathogenic (P/LP) variants using a 48-gene panel (32). Another Danish DCM cohort of 109 patients found that 44% carried P/LP variants (33). Most studies have found that few genes contributed to the majority of variants (34,35). This disparity between the positive yield in this Greenlandic population may have several explanations. First, it is possible that the present cohort is more diverse than other DCM cohorts, thus representing a wider variety of phenotypes. Second, it is possible that the proportion of genetically caused DCM is smaller in Greenland owing to a larger contribution of non-genetic risk. Finally, it is possible that the genetic causes of DCM in Greenland are novel and not captured by the gene panel used in this study.

The genetic architecture of present-day Greenlanders show that the ancestral Greenlandic population has been isolated and small for thousands of years. As a result of this extreme population bottleneck, genetic drift and founder events have resulted in reduced genetic diversity. Thus, populations like the Greenlandic are important in genetic discovery studies as genes that cannot be robustly established as disease associated in larger populations can be identified in Greenlanders. In the present study, we limited our screening to known DCM-associated genes. Future larger studies in Greenlanders such as genome-wide association studies or segregation analyses utilizing extended families with DCM may be able to reveal whether genetic variation in novel genes is a cause of DCM in Greenlanders. The strength of genetic discovery studies in Greenland are perhaps best exemplified by the discovery of the *TBC1D4* variant, which explains more than 12% of the diabetes variance in Greenlanders, but has not been identified in other populations (15). These potentials highlight the importance of diversity in genetic studies. Currently, the vast majority of genetic studies are carried out in European variants, meaning that genetic knowledge from known (European) variants, are carried over into non-European studies, leading to a risk of overlooking novel or population-specific variants. Supporting this idea, a recent study involving DCM patients of African ancestry found that individuals with African ancestry are less likely to have clinically actionable variants in DCM genes compared to those of European ancestry, a disparity attributed to differences in genetic architecture and the lack of clinical and reference data including African ancestry (36). This scenario might mirror the relationship between Greenlandic and European ancestries. While the demographic history of Greenlanders has allowed some variants to segregate at high frequency, it also means that rare variants are expected to occur less frequently in the Greenlandic population than other populations. This is reflected in analyses of the mutation load in the Greenlandic population compared to the European population, which shows that while the genetic diversity is low, the mutation load of deleterious alleles in an additive genetic model is identical (37). Thus, it is possible that DCM-causing variants may have diminished in frequency over time, either as a result of non-selective genetic drift, or as a result of selective adaptation to the harsh Arctic environment, which may have favored individuals without physical limitations. This could result in the current prevalence of DCM in Greenland being caused by non-genetic factors, considering the rapid lifestyle changes in the last century, including the introduction of smoking, alcohol, and a carbohydrate-rich diet. However, the reported high incidence of non-ischemic HF in Greenland could imply that these lifestyle changes alone may not fully explain the prevalence of DCM (13), in turn, emphasizing the need to consider an alternative pathogenesis of HF in this unique population.

In this study, we identified a large proportion of VUS. This is in line with findings in general, with about half of variants in the ClinVar database being classified as VUS (38). As new knowledge emerges, VUS can be reclassified and, as such, it is possible that some disease-associated variants may be contained within the VUS category in this study. However, studies assessing VUS reclassification have found that VUS are most often downgraded to B/LB, rather than reclassified as P/LP (39,40).

We identified a single variant classified as likely pathogenic, the MYH7 variant p.K637E. While this variant is not catalogued in dbSNP, it has been found previously. Møller and colleagues found the variant in a family of idiopathic dilated cardiomyopathy with variable phenotypes ranging from one individual with no echocardiographical abnormalities to two individuals requiring heart transplants (29). The two individuals in this study carrying the variant had reduced LVEF at early age. The K637 residue is highly conserved (29) and is located within a mutational hotspot which has been shown to cluster in hypertrophic cardiomyopathy (29).

Strengths and limitations:
This study utilizes extensive data from the unique, nationwide EMR. It includes detailed descriptions of echocardiography findings, patient comorbidities, and results from both CCTA and invasive coronary angiography. However, the observed low frequency of pathogenic variants observed in our study may partly be attributed to the inclusion of patients without DCM. This could be due to not establishing hypertension, a known cause of myocardial abnormality, as an exclusion criteria (2), resulting in inclusion of individuals whose heart failure might be secondary to conditions known to cause HF, rather than being DCM. Additionally, despite using the comprehensive EMR, there is a possibility that participants were incorrectly categorized as having DCM. This misclassification could be due to incomplete data in the EMR, influenced by the limited accessibility to healthcare and resources in Greenland. Future research may benefit from implementing more stringent exclusion criteria, particularly in distinguishing causes of HF. This approach may help ensure a more homogeneous study cohort consisting of genetic DCM cases.

Conclusion

In this study, we find a low prevalence of pathogenic and likely pathogenic variants within known DCM-associated genes in Greenlandic idiopathic heart failure patients. This finding underscores the importance of expanding genetic discovery studies to include diverse populations for a more comprehensive understanding of the genetic and non-genetic causes of DCM.

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Figures:

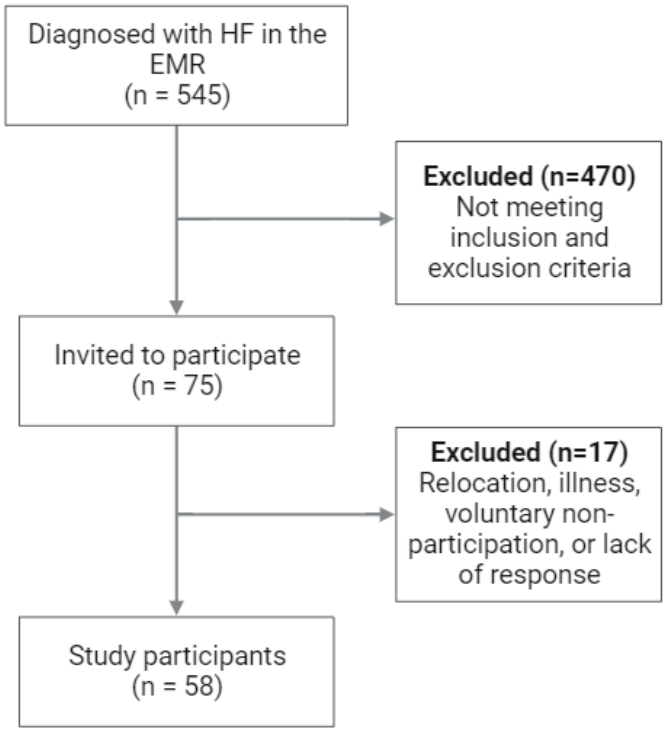

Figure 4: Participant recruitment flowchart outlining the progression from diagnosis with HF in the EMR to final study enrollment.

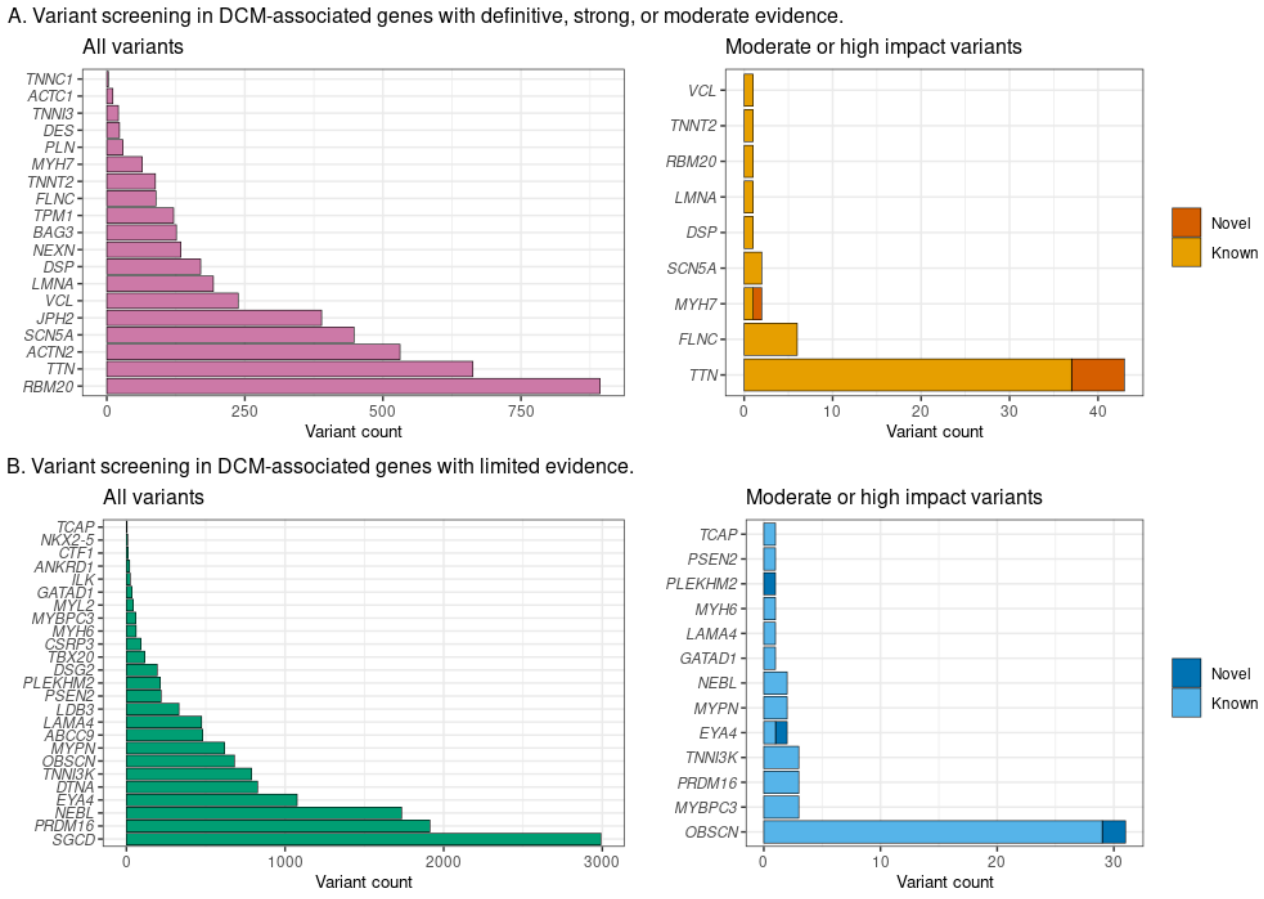

Figure 5: A) Screening of 19 genes curated for dilated cardiomyopathy variants classified with definitive, strong, or moderate, evidence with all identified variants in the left panel, and variants with a high or moderate predicted functional impact in the right panel. B) Screening of 25 genes with limited evidence of association with DCM with all identified variants in the left panel, and variants with a high or moderate predicted functional impact in the right panel. Novel variants are variants without a dbSNP id.

	Total; n = 59
Male sex, %	36 (61%)
Age at diagnosis, years ±SD	48.1 ± 10.2
LVEF in % ±SD at diagnosis	22 ±9
Measured at time of study:	
Age, years ±SD	53.1 ±10.0
BMI in kg/m^2 ±SD	31.8 ±7.3
BMI >30 kg/m^2, %	32 (59%)
HbA1C ≥48 mmol/L	17 (29%)
Pro-BNP in mmol/L	40.6 ±84.4
Family with HF (self-reported), %	17 (29%)

Table 1. n (%), Mean ±SD. LVEF: left ventricular ejection fraction, BMI: Body-mass-index, HF: Heart failure

Table 1. Characteristics of study cohort, at time of diagnosis and at time of this study.