Who are people who have heart failure as their first cardiovascular event in New Zealand

Hui Xu

A thesis submitted in fulfilment of the requirements for the degree of Master of Public Health, The University of Auckland, 2022

Abstract

Background

Heart failure (HF) has placed a great burden on the people of New Zealand (NZ) as well as its healthcare system. In NZ approximately 20% of first hospitalisations for CVD are due to HF, but the characteristics of those whose first presentation of CVD is for HF as opposed to another type of CVD are unclear.

Aim

To compare the characteristics of people whose first CVD hospitalisation was due to HF with those presenting with other types of CVD.

Method

A scoping review was carried out to explore how previous studies have identified and defined people with HF and described their characteristics. In addition, a cohort study was undertaken of people without CVD who had CVD risk assessment using the PREDICT electronic decision support programme in NZ. Data from participants' CVD risk assessment were linked using an encrypted National Health Identifier to data from regional and national health data collections. Participants who developed a CVD event during follow up were identified and were classified according to the type of CVD event and their characteristics at the time of CVD risk assessment compared. Among patients who had HF as their first CVD event during follow up, the proportion with subsequent coronary heart disease (CHD)-related admissions in the following year were estimated.

Result

The scoping review found that a wide range of methods have been used to define HF and baseline characteristics. ICD codes and medical chart review were used most often to define HF, while clinical assessments, self-report information, EHR and administrative data were the sources used to define baseline characteristics.

The cohort study found that, regardless of sex, people whose first presentation of CVD was due to HF were more likely to be of Māori or Pacific ethnicity, live in the most deprived areas, have obesity, diabetes, atrial fibrillation, valve disease or an implanted cardiac valve prosthesis or device, in comparison with those whose first presentation of CVD was due to a different

type of CVD. The proportion of HF patients who had CHD-related subsequent admissions within a year was only 4.1%.

Conclusion

Given the differences in characteristics at CVD risk assessment between patients whose first CVD presentation is HF as opposed to a different type of CVD, consideration should be given to the addition of HF-related factors to standard CVD risk assessment, particularly given the low proportion who subsequently present with CHD.

Acknowledgements

I would like to express my deepest gratitude to my supervisors Associate Professor Katrina Poppe and Dr Vanessa Selak for their precious expertise and knowledge. Their consistent encouragement and guidance carried me through all stages of the research. Thank you for suggesting different strategies in order to better support me.

Secondly, I would like to convey my gratitude to the team at the Vascular Informatics using Epidemiology and the Web (VIEW) team for creating such a wonderful research environment and allowing me to access the data. Especially, thanks to Dr Claris Chung and Yeun-Hyang (Catherine) Choi for cleaning and merging the PREDICT data and answering all my questions.

Finally, I am deeply grateful to my parent and friends. Thanks to my mum for her unconditional love, support and for believing in me through all the ups and downs. Thanks to Sharon, my best friend, for setting such a great example. Thanks to DM for providing me with a different view of myself throughout the learning journey.

Table of Contents

List of Figures

List of Tables

Abbreviations

AC	arrhythmogenic cardiomyopathy
ACVD	atherosclerotic cardiovascular disease
AF	atrial fibrillation
BMI	body mass index
CABG	coronary artery bypass graft surgery
Cevd	cerebrovascular disease
CHD	coronary heart disease
CRT	cardiac resynchronisation therapy
CVD	cardiovascular disease
DBP	diastolic blood pressure
DCM	dilated cardiomyopathy
DM	diabetes mellitus
eGFR	estimated glomerular filtration rate
Hba1c	haemoglobin A1C
HCM	hypertrophic cardiomyopathy
HDL	High-density lipoprotein
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HS	haemorrhagic stroke
ICD	Implantable cardioverter defibrillator
ICD	The International Classification of Diseases
ICD-10-AM	International Statistical Classification of Disease and Related Health Problems, Tenth Revision, Australian Modification
ICD-10-CM	International Classification of Disease (ICD)-9-Clinical Modification
IQR	interquartile range
LV	left ventricular
LVH	left ventricular hypertrophy
MI	myocardial infarction
NHS	National Health Service
NZ	New Zealand
NZDep	The New Zealand small-area index of relative socio-economic deprivation
PVD	peripheral vascular disease
RCM	restrictive cardiomyopathy
SBP	Systolic blood pressure

SD	Standard deviation
SGLT2	sodium-glucose cotransporter 2
TC	total cholesterol
TIA	transient ischaemic attack
UK	United Kingdom
USA	The United State of American

1 Chapter 1. Introduction

1.1 Rationale for thesis

Due to the enormous number of people affected and an exponential increase in hospitalisations, heart failure (HF) has been defined as a global epidemic and a major public health issue (1). The worldwide prevalence of HF has been increasing over the last three decades and will continue over the next ten years due to the ageing population (2). Despite the decrease in age standardised incidence of HF, rising rates in the young population have been observed in both New Zealand (NZ) and internationally (1,3). The prevalence of HF was 2.1% in NZ and HF health expenditures were considerable taking up almost two percent of the total health budget in NZ (4,5). Chan has shown that approximately 20% of the first presentations to hospital for CVD is due to HF (6). However, the characteristics of people whose first CVD hospitalisation is due to HF as opposed to another type of CVD has not been explored in NZ.

CHD is a condition of an imbalance between myocardial blood supply and demand and thus leading to myocardial ischemia which can negatively impact on the systolic and diastolic function and contribute to the development of HF (7). While CHD is considered as the most common cause of HF in some developed countries , in the study conducted by Khan et al., it has been shown that a third of HF cases developed prior to CHD (8). Chan also demonstrated an increase in the incidence of HF in patients without a history of CHD in both the young age group (<50 years) and the 50-70 years age group in NZ (6). However, to which degree the causes of their HF presentation is associated with CHD is also unclear.

In regard to the aspect of HF prevention, except for the prevention in the population level through initiatives, such as smoking cessation and management of obesogenic environment, routine cardiovascular disease (CVD) risk assessment has also been used as a prevention strategy of HF (9–11)(12). CVD refers to diseases which affect the heart and the blood vessels of the body. Therefore, HF is included as a type of CVD (13). The CVD risk assessment is for the 30-74 age group who do not have a history of CVD and it is a screening tool that estimates the risk of incident CVD (12). In order to assess the risk, different variables are required to be measured including socio-demographic factors, smoking status, diabetes status, family history of premature CVD, history of atrial fibrillation, BP, and the ratio of total cholesterol to high density lipoprotein cholesterol concentrations (TC/HDL) and the use of vascular medications. Although HF and atherosclerotic cardiovascular disease (ACVD) which refers to CVD caused

by atherosclerosis including coronary heart disease (CHD), cerebrovascular disease (Cevd) and peripheral vascular disease (PVD) share some of the risk factors mentioned above, other risk factors of HF are not included in the assessment, such as history of cardiomyopathies and history of valvular disease (13). Considering the differences between HF and ACVD in terms of their aetiology, it is important to figure out whether the CVD risk assessment is sufficient for HF prevention. By comparing the baseline characteristics of people whose first CVD presentation is HF and people whose first CVD presentation is a different CVD event, the differences in risk factors can be better detected.

This thesis sought to address gaps including the unclear differences between the characteristics of those whose first presentation of CVD is for HF and those whose first presentation of CVD is for another CVD and to which degree the causes of their HF presentation is associated with CHD by describing the characteristics of these patients using epidemiological methods.

1.2 Aim

To compare the characteristics of people whose first CVD hospitalisation was due to HF with those presenting with other types of CVD in order to gain a better understanding of the differences in their characteristics and the sufficiency of CVD risk assessment for HF prevention.

1.3 Objectives of the scoping review

Given the consideration that the findings of observational epidemiology studies can be affected by many factors including the origin of the data, in order to choose and analyse the appropriate sources of epidemiology data that are relevant for the quantitative analysis of this thesis, the following objectives will be met.

1. To find out how studies have defined HF
2. To find out how the baseline characteristics of the participants were defined

1.4 Objectives of the quantitative analysis

1. To describe the characteristics of HF patients including demography, comorbidities, clinical characteristic and cardiometabolic medication

By describing the characteristics of HF patients, the risk factors of HF as the first presentation of CVD can be better understood.

2. To compare characteristics between patients who had HF as their first CVD event and patients who had other atherosclerotic disease, haemorrhagic stroke or cardiac fatal event as their first CVD event

This can be a way to estimate the differences in risk factors for patients who had HF as their first CVD event as opposed to those that were presented with other CVD, which enables the sufficiency of CVD risk assessment for HF prevention to be better examined.

3. To estimate the proportion of patients who had HF as their first CVD event and had subsequent admissions associated with CHD within one year

As CHD is considered to be the most common cause of HF in developed countries, one of the hypotheses of this thesis is that people whose first CVD event being HF may represent a group of people who have undiagnosed CHD. By estimating the proportion of HF patients who experienced readmission relating to CHD within a year, it is possible to assess the proportion of people whose first CVD presentation being HF which was likely caused by CHD.

1.5 Hypotheses

1. Hypothesis 1: There are differences between people who developed HF as their first CVD event and people who developed other CVD
2. Hypothesis 2: People whose first CVD event as HF may represent a group of people who have undiagnosed CHD

1.6 Outline of thesis

This thesis consists of five main chapters, starting with this chapter (chapter 1), which focuses on the rationale, aims and objectives, and hypotheses of the thesis.

Chapter 2 describes HF including its aetiology, classification, risk factors, relationship with CVD, epidemiology and management.

Chapter 3 presents the scoping review with its methods and results.

Chapter 4 explains the method used for the quantitative analysis.

Chapter 5 presents the results of the quantitative analysis of the New Zealand data.
Chapter 6 discusses the main findings of the quantitative analysis and compares these findings with that of the scoping review. This chapter also provides the strengths and limitations of the thesis and its implications for the health sector and future research.

2 Chapter 2. Background

This chapter introduces heart failure in terms of its aetiology, classification and risk factors. The relationship between cardiovascular disease, atherosclerotic cardiovascular diseases and heart failure is also demonstrated. By discovering the epidemiology of heart failure internationally and in New Zealand and the management of heart failure, the understanding of HF is enhanced.

2.1 Definition of heart failure

Heart failure (HF) is a complex clinical syndrome with typical symptoms and signs and there is no single test which can diagnose HF(14,15). It is caused by the structural or functional impairment of ventricular filling at the normal pressure or ejection of blood sufficiently to meet the needs of the metabolising organs (14,15).

2.2 Aetiology of heart failure

It can be challenging to ascertain a specific cause to HF in an individual, as the causes of HF can be mixed and not mutually exclusive, suggesting that it is common for people with HF to have multifactorial aetiology (16). There are a wide range of aetiologies including ischaemic heart disease, hypertension, cardiomyopathies, valvular disease, arrhythmias, infections and cardiotoxic drugs (17).

Coronary heart disease (CHD) is a condition in which there is an imbalance between myocardial blood supply and demand, thus leading to myocardial ischemia (18). The occurrence of myocardial ischemia is virtually always caused by a degree of coronary obstruction which is due to the accumulation of atherosclerosis plaque (7,18). Coronary atherosclerosis can damage the myocardium by decreasing perfusion (19). While the regional dysfunction occurs at the injury site, the ventricle can be subsequently remodelled in myocardial segments which are distant from the site of scarring (19). This regional remodelling can distort the ventricular structure and result in the further dysfunction of the ventricle. When the ventricle dilates, it advances annular dilation, which can lead to mitral regurgitation and therefore be prone to HF (7). In addition, the chronic hypoperfusion caused by coronary atherosclerosis can lead to the reduced blood flow and glucose uptake in myocardial regions, which can negatively impact both the systolic and diastolic function. As a result, HF is developed (7).

Coronary atherosclerosis is the crucial determinant of the development of myocardial infarction (MI), which can also play a significant role in the pathogenesis of HF (7). The acute MI can cause the permanent death of cardiac muscle. As the infarcted tissues lose the power of movement, there can be insufficient relaxation during ventricular diastole and weakened contraction during ventricular systole (7,19). In addition, myocyte hypertrophy and myocardial fibrosis which cause progressive ventricular remodelling can occur in the infarcted segment and therefore the cavity can be dilated. These changes can all contribute to the development of HF (7,19).

Hypertension can increase myocardial mass and remodel the structure of the left ventricle (LV) by exposing cardiac myocytes to elevated mechanical stress and neurohormones (20). The left ventricular hypertrophy (LVH) and stiffness caused by constant volume and pressure overload can therefore impair the function of LV to fill with blood and eventually develop HF, even without the presence of obstructive epicardial coronary arteries (20).

Cardiomyopathies are defined as diseases of the heart muscle which are not secondary to coronary disease, hypertension or congenital, valvular, or pericardial disease and have known genetic or phenotypic patterns (16,21). They can be classified into four groups including dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), arrhythmogenic cardiomyopathy (AC) and restrictive cardiomyopathy (RCM) (21). DCM is characterised by the dilatation of the left ventricle. In terms of the histological characteristics, cardiomyocytes are hypertrophied with increased extracellular fibrosis and loss of myofibrils (21). HCM is characterised by inappropriate myocardial hypertrophy, which can cause obstruction of the LV outflow tract(21). In AC, the ventricular myocardium is replaced by progressive fibrofatty deposits that create an arrhythmogenic substrate (21). In RCM, the filling and diastolic function of ventricle is impaired although the systolic function and ventricular wall thickness is relatively normal (21). Although each of them can cause the development of HF, DCM is a more common cause compared to the other categories (21).

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and shares common pathophysiologic processes with HF (22). Hence, although AF can be the consequence of HF, it can also cause HF. The impairment of LV filling can be caused by the loss of atrial systole in AF, which can result in up to 25% of decreased cardiac output (22). In addition, as the

ventricular conduction is abnormal and/or rapid in AF, LV dysfunction can occur (22). These mechanisms can all promote the development of HF.

Infections can lead to toxic metabolic effects including relative hypoxia and acid base abnormality, and with the presence of peripheral vasodilation and tachycardia, the demand of myocardial oxygen will increase (23). In this way, infections may lead to HF.

The causes of HF can be distinctly different between high-income regions and low-income regions. While coronary heart disease and hypertension are the most common cause of HF in developed countries, valvular heart disease and cardiomyopathy are more common in the developing world (16). A systematic literature review which studied HF epidemiology demonstrated that more than 50% of HF incidences could be attributed to CHD in North America and Europe (24).

2.3 Classification of heart failure

The American College of Cardiology Foundation (ACC) has constructed a staging system which identifies four stages to demonstrate how HF can develop and progress from one stage to the next, and therefore how it should be managed. Based on the recognition of the risk factors and structural prerequisites for the progression of HF, Stages A and B focus on identifying patients who are prone to developing HF (25,26). Therefore, Stage A patients are considered as those who lack symptoms of HF or structural heart disease but are at high risk for HF as they have hypertension, diabetes mellitus or other risk factors, whereas patients who demonstrate structural heart disease but do not have symptoms of HF are grouped into Stage B (25,26). Stages C and D are overt HF (6). Stage C designates patients with underlying structural heart disease and current or prior symptoms of HF, and Stage D patients with refractory HF and who need specific interventions (25,26). The progression of HF would either not move forward at all or move along the stages from one to the next, unless development of HF was slowed or prevented by medical interventions. It would be deemed abnormal if there is a spontaneous reversal of this development (25,26).

The criteria for grouping patients into stage A and B might shed light on the precipitating event which has happened to patients who have HF as their first cardiovascular disease event.

2.4 Risk factors for heart failure

According to the staging system developed by the ACC, except for the risk factors including hypertension and atherosclerotic disease explained above, there are other risk factors which can also predispose an individual to HF. These risk factors are diabetes mellitus, obesity, LVH and valvular disease (1).

The development of heart failure can be attributable to diabetes mellitus (DM) via systemic, myocardial and cellular mechanisms (27). For example, by causing the proliferation and inflammation of the vascular smooth cells, hyperglycemia and hyperinsulinemia speed up atherosclerosis, which then lead to the occurrence of myocardial ischemia and thus HF (27). Other than causing CHD, hyperglycemia can also lead to LV hypertrophy through forming advanced glycation end products which can increase fibrosis. As a result, the myocardium becomes stiff and cardiac relaxation is impaired, and with the exacerbated diastolic dysfunction, HF develops (27).

Obesity is also associated with HF. Due to the excess adipose tissue and fat-free mass, obese people's metabolic demands increase, which contributes to increased total blood volume and cardiac output (28). This makes venous return to the right and left ventricles increase, increasing wall tension and dilating the ventricles (28). These changes lead to hemodynamic overload and eventually failure of the LV. While LV changes can increase right ventricular (RV) afterload to remodel RV structure and cause RV to fail, obesity hypoventilation syndrome can also result in hypoxia-induced vasoconstriction and pulmonary hypertension and eventually cause RV failure (28). In addition, tissue degeneration and inflammatory response which is associated with obesity can lead to myocardial fibrosis and the development of LVH. Hence, the cardiac function is impaired (28) .

LVH is a risk factor for HF (29). The anatomical changes including perivascular and myocardial fibrosis, medial thickening of intramyocardial coronary arteries and myocyte hypertrophy are involved in LVH. These changes can disturb myocardial blood flow and impair diastolic function which can directly relate to HF (29).

Patients with asymptomatic valvular disease are also more likely to develop HF. Aortic stenosis is a condition where the blood is restricted to flow from the LV to the aorta due to the narrowing of the aortic valve opening (30). In patients with valvular AS, the thickness of their LV wall

increases while the LV chamber size is maintained and this compensated hypertrophy is to normalise the stress of the LV wall (30). However, as the pressure continues to overload, the compensatory mechanism will eventually fail which can impair the systolic function and cause HF (30).

2.5 Relationship between cardiovascular disease /atherosclerotic cardiovascular disease / heart failure

The cardiovascular system consists of the heart and a network of blood vessels which allow blood to flow between the heart and the peripheral tissues. Hence, generally speaking, cardiovascular disease refers to diseases which have an impact on the heart and the blood vessels of the body and it includes CHD, Cevd, PVD, HF and haemorrhagic stroke (HS) (31). The aetiology of CVD can vary from chronic fatty changes, infections, genes to trauma and one classification of CVD is based on the involvement of the deposition of fatty plaques which is also known as atherosclerosis and can make the localised wall thicker and narrow the blood vessels (32).

CVD caused by atherosclerosis which results in the reduction or the loss of blood supply distal to the plaques is referred to as ACVD (32). As the atherosclerotic plaque can be formed anywhere in the body, besides CHD that has been mentioned earlier, there are two other major conditions based on their anatomical location: Cevd, including ischaemic stroke and transient ischaemic attack (TIA); and PVD(4). ACVD can be a risk factor for HF, and as a major type of CVD, HF shares various common risk factors with ACVD including hypertension, smoking, diabetes mellitus, obesity and family history of premature CVD (33). These risk factors facilitate the formation of fatty streaks, the progression of atheroma and thus the formation of atherosclerotic plaque to cause ACVD and contribute to remodel the structure of the heart to cause HF (19,27,28,34).

For other diseases mentioned above in the HF aetiology section, such as valvular disease, infiltrative cardiomyopathies, and cardiac arrhythmias, they are other major types of CVDs known as non-atherosclerotic CVDs (31).

2.6 Epidemiology

2.6.1 Epidemiology of heart failure internationally

According to the systematic analysis conducted by the Global Burden of Disease 2017 Disease and Injury Incidence and Prevalence Collaborators for 195 countries and territories from 1990 and 2017, it was estimated that there are 64.3 million people living with heart failure throughout the world and the estimated prevalence for the general adult population in developed countries was one to two percent (35). On the basis of the data from the National Health and Nutrition Examination Survey (NHANES) from 2011 to 2014, 6,500,000 participants reported "ever having congestive HF" which made the estimated HF prevalence in the USA to 2.5 percent (36). Using data from NHANES and the projected population counts for the years 2010 to 2030 obtained from the US Census Bureau, the number of people with HF was projected, where an extra 3 million people are expected to have HF by 2030, in comparison to 2010 and this means that the prevalence will be increased by 25 percent (37).

Based on the healthcare claims data from 2009 to 2013 obtained from over three million inhabitants, the prevalence of HF was four percent in Germany (38). By collecting data from a morbidity registration network from 2000 to 2015, a Belgium study estimated the prevalence at 1.2% in men and 1.3% in women (39). A population-based study using primary care data of 4 million individual showed the prevalence of 1.6% in the UK (40). A systematic review which studied the reported prevalence from 1990 and 2015 showed that the range was between 1% to 2% in Australia, but echocardiographic and biomarker studies showed the prevalence of 5.3% in Indigenous communities (41). However, epidemiological data from less developed countries was lacking. Scarce literature showed that Asia had similar prevalence to developed countries as it is 1 to 1.3 percent. No population-based studies were found estimating prevalence in Northern and sub-Saharan Africa (42).

Nevertheless, Groenewegen et al. state that while the "gold standard" for diagnosing HF is lacking, pre-defined echocardiography criteria appears to be a suitable method to validate cases (42). A systematic review which included echocardiographic screening studies, thus also counting previously unrecognised cases, showed that the "all type" HF prevalence was 11.8% among people aged 65 years and over in Western countries. This would result in an estimated prevalence of 4.2% in the general population (43). Although the heterogeneity of methods across studies needs to be underscored in this meta-analysis, the difference between 4.2% and

2% which came from the calculation based on the only established cases suggested that not all HF cased were detected (42).

Regarding incidence rates, Groenewegen et al., reported that in developed countries, the incidence rates of HF among adults aged above 55 have been stable between 1970 and 1990 and are even decreasing now, but the rates among younger individuals (aged 18-55) has been steady or has even increased (42). The drop was noticeable in a community-based study where the population was representative of the Upper Midwest region of the US, with the age- and sex-adjusted incidence decreasing from 3.2 to 2.2 cases per 1000 person-years between 2000 and 2010 (44). In the UK, based on the electronic health records of four million individuals, it was observed that the adjusted incidence rates of all-type HF dropped seven percent between 2002 and 2014 from 3.6 to 3.3/1000 person-year. However, there was an increase in the incidence in younger (<55 years) and very old patients (>85 years), which contributed to a two percent increase in the crude incidence (40). In Denmark, after analyzing the data collected from three nationwide Danish registries between 1995 and 2012, a similar trend was noticed as a declined incidence of HF was found among older adults yet increased among younger people with the percentage of young patients (≤50) having incident HF doubled from 3% to 6% within this period (45).

Although a significant decline in the mortality rate had been noted in the United States from 2006 to 2009, there was not much change after 2009 (46) . A study in Norway showed the mortality rate from HF declined slightly (47). In Germany, the in-hospital mortality rate remained stable (48). Overall, the data shows that the mortality of HF has remained unchanged worldwide (46).

Health failure inequities exist between countries, race, ethnicity, and sex. On average, people in the low and middle income countries are more likely to experience HF seven years earlier than those in the high income countries (49). Disparities in the incidence of HF was also observed in multiethnic cohorts, for example, in the CARDIA (Coronary Artery Risk Development in Young Adults) study, the incident and mortality rates in young Black adults were estimated to be two to three times higher than that of young White adults (50). According to the American Heart Association, the prevalence of HF in African-Americans and Hispanics were at least 0.3% to 1% higher than that of Whites and African-American women had the highest prevalence of HF among all intersection of race and sex in the US (26).

The worldwide prevalence of HF has showed an increasing trend in the last 28 years and it is unlikely to reverse in the next ten years (2). This worldwide prevalence is directly linked to a 346.17 billion US dollar expenditure and 9.91 million years lost due to disability (YLDs); 4.6 million and 5.3 million YLDs were distributed among males and females, respectively. The increase in the global number of HF YLDs was 106.0% compared with 1990 (2). The age-standardised YLD rates of HF were highest in countries with a high socio-demographic index (SDI) quintile in 1990 while that of HF were lowest in countries with a low SDI. However, the burden distribution was opposite in 2017, as there was a significant increase in age-standardised YLD rates of HF in countries in the low SDI quintile (51). By the year 2030, both the prevalence and YLDs in people aged ≥80 years will increase over 30%, which can lead to a higher rate of hospital readmissions, resulting in higher inpatients costs and a higher usage of healthcare resource for managing HF in the next 10 years (2).

2.6.2 Epidemiology of heart failure in New Zealand

According to the latest New Zealand Health Survey, the prevalence of self-reported HF was 1.6% during 2020 and 2021, which is an estimated 66,000 adults (52). On the basis of data collected from the NZ PREDICT programme which was established to investigate aspect of CVD and assist health professionals to assess and manage CVD risk in routine practice, a cross-sectional analysis involving nearly 500,000 participants assessed between 2004 and 2016 estimated that the prevalence of HF was 2.1% in New Zealand (53,54). The total health expenditure was $ 38.8 billion from 2009 to 2016 and the overall expenditure of HF took up 1.5-2% of total health budget in New Zealand, which demonstrates the great burden that HF placed on the people of NZ and NZ healthcare system(4,5).

Chan et al. investigated the trend of HF incidence among NZ residents from 2006 to 2018 and 116,113 hospitalisations due to incident HF were identified over this period (3). There was a decline in the age-standardised incident rate from 403 to 323 per 100,000 between 2006 and 2013, which was consistent with the decreasing trend between 1998 and 2008 reported by Wasywich et al. who conducted a population analysis based on all HF hospitalisations and mortality data in New Zealand (3,55). The decrease then plateaued between 2013 and 2018. While this pattern can be clearly demonstrated in men, the constant decreasing trend in age-standardised incident rate was demonstrated in women from 2006 to 2018 (3). In term of age-specific rates of incident HF hospitalisation, between 2006 and 2018, an increase of 1.5% per

year in rates was observed in individual aged 20-49 years old, from 22 to 30 per 100,000 and a decrease of 1.2% per year in rates was observed in patients aged ≥80 years old, from 3061 to 2565 per 100,000 (3).

The New Zealand mortality trend was examined by Wasywich et al. for the period between 1998 and 2008. It was found that over the two decades, mortality rates were decreasing significantly, in-hospital mortality decreased from 14.2 to 6.5%, 30-day mortality from 15.2 to 9.3, and 12-month mortality from 39.0 to 28.1% (55). While gender did not have an impact on mortality, age had a heavy influence on it as a two to three times higher mortality rate was observed in patients aged ≥75. These declining trends continued between 2010 and 2015 (55). After following HF hospitalisation in Australia and New Zealand, a population-wide study found the 30-day mortality declined from 12.5% to 8.1 percent (56).

Disparities for heart failure are high in New Zealand in terms of ethnicity and socioeconomic deprivation. According to the latest self-reported data, the Māori population had the highest prevalence of 2.3% from HF, while the prevalence of HF among Asian and European population was as low as 0.4% and 1.7%, respectively (52). On average, Māori can experience HF 10-15 years earlier than Non-Māori. The mortality rate among Māori patients was more than two times higher than that of Non-Māori, and the hospital admissions for HF were four times higher among Māori compared with Non-Māori (13). An excess hospitalisation rate was observed for Māori females who were about 4.5 times higher than that of non-Māori females (13). Disparities in the prevalence of HF according to socioeconomic status are also evident. The highest self-reported prevalence of 1.9% has been seen in the most deprived area while the least deprived area has the lowest prevalence of 1.2 percent (52). In terms of mortality and hospital admissions, an analysis of HF mortality and hospital admissions showed a strong association between socioeconomic deprivation and heart failure (57). Using NZDep which measures a small area deprivation with decile 1 representing the least deprived and decile 10 the most deprived, it was observed that with an increase of one NZDep decile, the HF mortality and hospitalisations rates increased by 11 percent (57).

2.7 Management of heart failure

2.7.1 Stage A heart failure

People with Stage A HF are identified due to their established risk factors associated with HF and no structural heart disease (15). Primary prevention aims to leave no space for the development of structural heart disease in the form of a MI and adverse LV remodeling (58). By changing lifestyle and using pharmacotherapy, an acceptable level of BP, blood glucose and lipid control can be achieved and by stopping smoking, exercising regularly, and minimising alcohol and illicit drug intake, risk factors for HF can be managed (58).

2.7.2 Stage B heart failure

Patients with Stage B HF may have one or more forms of structural heart disease including, abnormalities of LV geometry, LV systolic dysfunction, LV diastolic dysfunction, and previous MI(15). Secondary prevention aims to detect patients with asymptomatic structural heart disease and halt the development of symptomatic HF by allowing suitable interventions such as BP lowering medication and ACE inhibitors for patients on the basis of LVH(58). Hence, screening for pre-clinical HF has been considered for ambulatory patients with high risk. 12-lead electrocardiography (ECG), echocardiography, and plasma B-type natriuretic peptide (BNP) or N-terminal proBNP (NT proBNP) can be used to detect abnormalities in cardiac structure and function (58). Nevertheless, due to the uncertainty of the cost-effectiveness, there is currently no recommended population screening for Stage B HF worldwide (58).

2.7.3 Stage C heart failure

Patients with Stage C HF are defined as having more advanced disease with present or past symptoms (15). The management goal for these patients is to slow or stop HF disease progression and limit disability due to HF through managing the symptoms of HF and tackle the underlying disease process (58). Management of stage C HF has been developed over the years. The management can be different by the classification of HF including heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). Patients diagnosed with HF can be categorised into HFrEF or HFpEF based on the measurement of LV ejection fraction (LVEF) which represents the percentage of total ventricular volume that can be ejected from the heart per heartbeat (14,59,60). The definition HFrEF and HFpEF can vary depending on the guidelines from different countries or

regions(14,59,60). While US and European guidelines define HFrEF as LVEF being equal or lower than 40%, the threshold for HFrEF is an LVEF <50% in Australia and NZ guideline. All these guidelines define HFpEF with an LVEF ≥50% (14,59,60).

In terms of the pharmacological treatments for patients with HFrEF, the general principles applied by all guidelines are to modulate the renin-angiotensin-aldosterone (RAAS), sympathetic nervous systems and natriuretic peptides by using renin-angiotensin system inhibition with angiotensin-converting enzyme inhibitors (ACE-I) or an angiotensin receptor-neprilysin inhibitor (ARNI) or an angiotensin II receptor blocker (ARB), beta-blockers and mineralocorticoid receptor antagonists (MRA)(14,59,60). The cornerstone therapies comprised by the triad of an ACE-I/ ARNI/ ARB, a beta-blocker, and an MRA have been shown to decrease mortality, reduce hospitalisation and reduce symptoms in patients with HFrEF(14,59,60). Nevertheless, the recommendation for the use of sodium-glucose cotransporter 2 (SGLT2) inhibitors, which are a class of glucose-lowering drug can be different among guidelines(61). While SGLT2 inhibitors were only recommended to patients with type 2 diabetes mellitus associated with CVD in Australia and NZ guidelines, considering the effect of reducing the risk of CVD mortality and preventing HF symptoms from worsening in patients with HFrEF, the US and European guidelines suggested to add SGLT2 inhibitors into the therapy for patients with HFrEF regardless of their type 2 diabetic status(14,59,60).

For selected patients with HF, device and interventional therapies were also recommended in conjunction with optimal medical therapy. All guidelines recommend cardiac resynchronisation therapy (CRT) and implantable cardioverter defibrillator (ICD) to manage patients with certain symptoms (14,59,60). Intraventricular and interventricular dyssynchrony can be caused by a left bundle branch block due to the occurrence of electrical remodelling in patients with HFrEF and this, in turn, worsens cardiac contractile performance (14,59,60). CRT aims to resolve or reduce this dyssynchrony by ensuring both the left and the right ventricles are paced simultaneously and as a result, the LV function is likely to be improved and cardiac remodelling can be impacted positively (14,59,60). Several studies have shown that CRT has better effects in decreasing hospitalisations and mortality compared to optimal medical therapy (62,63). Regarding the prevention of sudden cardiac death which is predominantly caused by electrical disturbances especially ventricular tachyarrhythmia, with the effect of restoring sinus rhythm by correcting potentially lethal ventricular arrhythmias, ICDs are suggested to be used for patients with HFrEF (14,59,60).

With regard to certain conditions, guidelines from Australia and NZ recommended other surgical management (14). Coronary artery bypass graft surgery (CABG) which aims to improve blood flow and oxygen supply to the heart by redirecting blood around a narrowed or blocked artery was recommended for patients with HFrEF due to aetiology of ischaemic heart disease and an LVEF ≤35% (14,64).

In terms of the treatments for patients with HFpEF, until recently, no therapies have been demonstrated as effective in reducing mortality and hospitalizations (14,59,60). Although there is no recommendation for the specific HFpEF-modifying treatment, considering the underlying hypertension and/or CHD in the majority of patients with HFpEF, ACE-I/ARB/ARNI, beta-blockers, or MRAs should be used for patients with these contributing comorbidities (14,59,60) . Other practice advice has been given based on all three guidelines, for example, in order to manage congestion, diuretics are recommended for use (14,59,60).

2.7.4 Stage D heart failure

Stage D patients are those with refractory HF(15). Except for maintaining or optimizing the guideline-directed medical therapies that are also indicated in patients with stage C HF during hospitalization, specialized treatment strategies are also recommended for patients with advanced HF(60). For example, considering the frequent presence of hyponatremia and diuretic-refractory congestion in stage D, fluid restriction is commonly prescribed(60). In addition, given its effect of maintaining systemic perfusion and preserving end-organ performance through stimulation of adrenergic or dopaminergic receptors and calcium sensitization, inotropic agents are recommended as a “bridge therapy” for patients who are awaiting advanced HF therapies such as mechanical circulatory support (MCS) and cardiac transplantation(60). While MCS can function either as a bridge to transplant or a long-term destination therapy by assisting the native heart, cardiac transplantation can improve survival and quality of life (60).

2.7.5 Risk-based strategy in New Zealand

NZ national guidelines have recommended a regular CVD risk assessment as the main risk-based strategy for preventing CVD and thus HF through managing individuals based on their estimated five-year CVD risk. Since 2003, CVD risk has been calculated based on the National Heart Foundation’s cardiovascular risk tables, or an electronic decision-support tool

established on the Framingham risk equation (4). The risk equation was modified to prevent the potential underestimation of CVD risk in certain groups, such as Māori, Pacific or Indian ethnicity (4). In 2018, the new CVD risk equations known as the NZ Primary Prevention Equations were created separately for men and women (4). In this version, NZDep, CVD medications and a past medical history of atrial fibrillation were included as new predictors (4). To calculate the five-year CVD risk, the equation was developed as: (1-Baseline survival function $^{\exp(\text{sum of (coefficients*variables)})}$)*100, which makes the result as a percentage (4). Variables which are required to be measured include age, ethnicity, NZDep, smoking status, diabetes status, family history of premature CVD, history of atrial fibrillation, blood pressure (BP), and the ratio of total cholesterol to high density lipoprotein cholesterol concentrations (TC/HDL) and the use of vascular medications (4).

For those who have a five-year CVD risk below five percent, they might not meet the threshold for the first treatment, considering that the expected benefits of treatment might not outweigh harms from therapy (4). For those who have a five-year CVD risk between 5-15%, drug treatment includes considering lipid-lowering and blood pressure lowering (4). For those who have a five-year CVD risk of 15% or above, their risk is considered to be comparable to the risk for people with a history of CVD and therefore their risk management and lifestyle modification will be more aggressive, such as weight management, and the use of statin and blood pressure lowering medication (4).

Since 2003, the assessment has been recommended for men aged 45 years or older and women aged 55 years or older (10 years earlier for a subset of population at increased risk including Māori, Pacific, and Indian ethnicity and people with known CVD risk factors (65). In the 2018 updated version, the recommended age for men and women to begin CVD risk assessment remained the same (10 years earlier for people with known CVD risk factors) (4). However, for subpopulations at increased risk, the recommended age to begin CVD risk assessment has been 15 years earlier than other population groups (4) .

2.8 Summary of background

The definition of HF in this thesis is outlined in this chapter. The wide range of etiology of HF including ischaemic heart disease, hypertension, cardiomyopathies, valvular disease,

arrhythmias, infections and cardiotoxic drugs has been overviewed. According to the criteria from ACC, the progression of HF is classified into four different stages, in which stage A and B demonstrates risk factors that make people prone to developing HF. As a major type of CVD, HF shares some risk factors such as obesity, diabetes, hypertension, and smoking with ACVDs, while ACVDs can also be a risk factor for HF. The worldwide epidemiology of HF has been discussed. With the worldwide prevalence of HF increasing over the last three decades, an enormous burden has been placed on the healthcare system and the trend is unlikely to reverse in the next decade. There are clear disparities between countries, races, and ethnicities around the world. Disparities for heart failure in terms of ethnicity and socioeconomic deprivation are also high in New Zealand, where the trends of HF incidence have been stable from 2013 to 2018.

Due to the heavy burden placed on patients and healthcare systems by HF, the increasing incidence of HF in patients without a history of CHD, and that approximately 20% of the first presentation to hospital for CVD in NZ is due to HF, there is a clear need to address the current knowledge gap regarding the characteristics of people who have HF as their first CVD presentation. Through filling the gap, the understanding of the characteristics of people whose first CVD presentation is due to HF can be gained and contribute to the improvement of clinical practice in the prevention, diagnosis and management of HF. Furthermore, the CVD risk assessment can be better examined in terms of its role in preventing HF.

3 Chapter 3. Scoping review

While the last chapter introduced HF in terms of its epidemiology and management, overviewed the etiology and risk factors of HF and provided the rationale for this thesis and why it focuses on people whose first presentation of CVD is due to HF, this chapter will address the objective of mapping the definition of HF and baseline characteristics of patients in studies which focus on the same study population through a scoping review. This chapter integrates the rationale of the scoping review, the method of the literature search, the findings of the scoping review and a discussion of the results.

3.1 Rationale

For observational epidemiology studies, it is widely acknowledged that the findings can be impacted by many factors, such as chance and uncontrolled confounding (66). However, a study showed that the findings of a meta-analysis can also be impacted due to an effect that involves modification as the data sources are investigated as a potential cause of heterogeneity (67). This highlights the relationship between the origin of the data and the study findings. Given that this is an observational epidemiology thesis with the aim to describe people whose first CVD presentation is due to HF, it is critical to understand how different types of data might affect the types of findings generated. Therefore, the appropriate sources of epidemiological data that are relevant for this thesis can be better chosen and the results derived from the quantitative analysis of the thesis can be better compared to the findings of other studies.

3.2 Background

Different sources of data are used to answer HF related epidemiological questions, including the primary data which is collected for research purposes and the secondary data which is collected for non-research purposes (68). While prospective observational studies, registries and interview data can be defined as primary data, secondary data includes paper-based health records, Electronic Health Record (EHR) data which contains various information including free text information from medical history and physical examinations, and administrative health data based on medical coding systems (68).

Medical coding classification systems are groups of codes that match up individual diagnoses and procedures and they are used for the accurate tracking of disease. The relevant data is

encoded through a manual coding process where clinical statements are reviewed and applicable codes are identified (69). Although physicians might conduct the code assignment, this is often carried out by coding professionals. Therefore, to have accurate clinical data, it is reliant on many aspects including the accurate documentation of the diagnosis in clinical notes and the accurate translation of the clinical documentation performed by the coders (69).

The International Classification of Diseases (ICD) system has been used for decades with its initial intention for classifying causes of death but gradually extending its scope to include the extent, causes and consequences of human disease (70,71). The ICD system is used in all venues of healthcare for health recording, for example, health outcomes can be coded based on discharge diagnoses including primary and secondary diagnosis. According to the ICD-10-CM Official Guideline for coding and reporting, the principal diagnosis is defined as "the condition, after study, which takes the main responsibility of admission to the hospital" and the secondary diagnosis is defined as "the co-existing conditions with the principal diagnosis at the time of admission or the conditions developed subsequently impact on the current inpatient admission" (72). It is important to be aware that these diagnoses might not be the particular reasons for the patient's admission (72).

While ICD can support many services, such as payment, in terms of the public health aspect, ICD facilitates the comparability of the data among regions and countries and allows for the long-term study of disease (70,71). The WHO has taken charge of the system since 1948 during which time the sixth revision of ICD was developed and after that the tool was revised every decade, the latest version, ICD-11, came to effect in 2022 (70,73). Due to the time frame, ICD-9 and ICD-10 is the most used tool to identify HF in recent studies. The ICD-10 is very different from ICD-9 in terms of structure and concepts (73). By adding new codes which conveyed more specific information about anatomic sites, etiologies, comorbidities, and complications, the level of specificity in ICD-9, it can be improved by the new classification codes in ICD-10. The increased granularity in ICD-10 will therefore allow for better disease tracking and better analysis of disease patterns (73). However, in terms of ICD-10 coding of HF, one of the major issues is that it does not disaggregate according to whether LVEF is reduced or not (74). The ICD-9 and ICD-10 coding of HF is 428 and I50 respectively (74). Other versions were developed based on ICD-10 including ICD-10-CM standing for the clinically modified version adopted by the US and ICD-10-AM used for the classification of admitted patient care in Australia (73).

Another frequently used coding system is Read which has been used in the National Health Service (NHS) in the UK and the codes represent HF are G58..00 (75) . While READ codes can be used in primary and secondary care, it is in widespread use in general practice in New Zealand due to its strength of allowing more detailed information relevant to the primary care setting, (75).

3.3 Objective

Accordingly, a scoping review of the current literature is conducted to examine the scope of work on HF as the first CVD event and map the key definitions underpinning the research area. The following research questions are formed: (1) how have studies defined HF? (2) and how the baseline characteristics of the participants were defined?

3.4 Methods

3.4.1 Study approach

The scoping review was reported according to the items recommended by the Preferred Reporting Items for Systematic Review and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR)(76).

3.4.2 Eligibility criteria

Based on the objectives of this scoping review, the inclusion criteria were constructed and these criteria were all required for studies to be considered in the scoping review:

- Studies involving participants who have HF as their first CVD event
- Studies including detailed information about how they define HF from the data
- Studies including detailed information about how they defined baseline characteristics from the data
- Population-based studies which means that the study participants are individuals drawn from the general population who have common characteristics, such as demographic features, or health conditions(77).

The following literature was excluded:

- Participants have previous CVD history at baseline

- Studies only focus on population groups who had specific pre-exiting diseases such as diabetes and chronic kidney disease
- Studies where the full text was not available in English
- Published prior to 2010, as those cannot reflect the most recent findings of HF

3.4.3 Information sources

The database Medline (Medical Literature Analysis and Retrieval System Online) was searched from 2010 to January 2022 in order to capture potentially relevant publications. The draft of the search strategies was formed with the assistance of experienced librarians and further polished by one of the supervisors (Vanessa Selak). The research was run in February 2022. After that, the reference lists of relevant documents were searched as well. The final searching results were exported into RefWorks, where the de-duplication process was conducted.

3.4.4 Search

Medical Subject Heading [MeSH] term including heart failure and free text including first present*, first manifest* and incident*. The search terms are demonstrated in the table below (Table 1).

Table 1 Medline literature search terms

#	Medline (Ovid)
1	("congestive heart failure" or "cardiac failure" or "myocardial failure" or "HF" or "heart failure").mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
2	Exp Heart Failure/
3	1 or 2
4	("first present*" or "first manifest*" or “first diag*” or “incident congestive heart failure” or “incident cardiac failure” or “incident HF” or "incident heart failure").mp
5	3 and 4
6	limit 5 to (English language and yr=”2010-current”)

Note: In Medline, the use of the asterisk in “first present*”will generate any alternatives of the keyword “first present”.

3.4.5 Study selection

The citations which were detected based on the search strategies and as identified from reference lists were exported to Refwork and the duplicates were removed. The same de-duplication process through Refwork was conducted for further relevant articles from the reference lists of the reviewed articles. All titles retrieved by the literature search were reviewed and the abstract of articles which appeared potentially relevant to the study area were screened. Finally, full papers were screened according to the study’s inclusion and exclusion criteria (as noted previously) if their abstracts were considered suitable.

3.4.6 Data extraction and synthesis

Data extracted from all included articles included article characteristics (e.g., author, country of origin, year, origin cohort), characteristics of study population, sample size, recruitment, study aim, definition of HF, definition of baseline characteristic of patients, data source, report on other CVD, comparison. Charting was used to synthesize data by sifting and sorting materials by key issues. To answer the research questions of scoping review, charting was grouped on basis of datasets for definition of HF, definition of baseline characteristics of patients, data source and recruitment.

3.4.7 Critical appraisal

A critical appraisal of the quality of included studies is not a requirement for the scoping review. Nevertheless, relevant issues to the interpretation of findings were noted in the results of discussion section of the scoping review.

3.5 Results

3.5.1 Selection of sources of evidence

After duplicated records were excluded, 1176 publications were identified through electronic database searching and references in review articles (Figure 1). According to the title and abstract of articles, 757 and 327 publications were excluded respectively, which left 92 full text articles to be assessed for eligibility. Among these, 70 were excluded for the following reasons: seven only excluded patients with HF history, 17 did not mention whether patients with CVD

history were excluded, 10 did not give a detailed explanation of how they defined HF, and 37 did not give a detailed explanation of the way the baseline characteristics were defined. Hence, 21 studies were included for review.

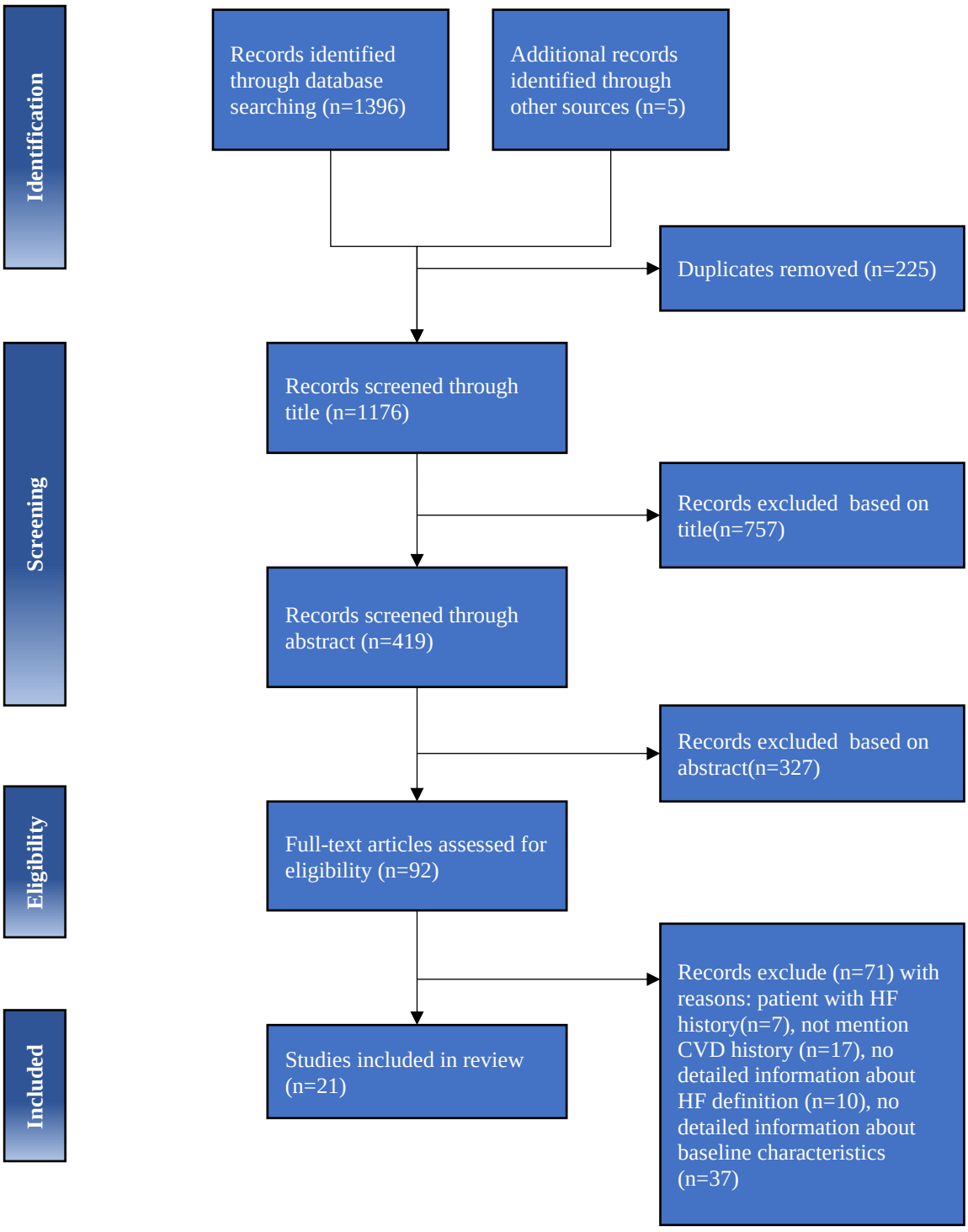

Figure 1 Prisma flow diagram showing the process used for screening studies

3.5.2 Characteristics of included studies

There were 14 datasets which developed 21 articles. Of the 21 articles, most (n=13) were conducted in the US (78–90), with four based on the Multi-Ethnic Study of Atherosclerosis (MESA) including one combining the Dallas Heart Study (DHS), two were based on the lifetime risk pooling project dataset (LRPP), two used Northwestern Medicine Enterprise Data Warehouse (NMEDW), two relied on the Veterans Affairs (VA) system, and the rest were from the Framingham Heart Study (FHS), the Coronary Artery Risk Development in Young Adults (CARDIA) and the Atherosclerosis Risk in Communities (ARIC) studies (n=3). As a result, there were eight US datasets included (Table 2). Of the 21 included articles, five were conducted in Europe and the UK (91–95), within which two were from the CArdiovascular research using LInked Bespoke studies and Electronic Health Records (CALIBER) programme and the rest were based on UK-Biobank, the Swedish Mammography Cohort (SMC) and the and the Rotterdam Study (RS) (n=3). Hence, two UK datasets and two European datasets were included (Table 2). The rest of the research (n=3) was developed in Asia (96–98), two used the Japan Medical Data Centre (JMDC) Claims Database and one was based on the Korean National Health Insurance Service-National Sample Cohort (NHIS-NSC), which stood for the two different datasets. The sample sizes of these studies ranged from 4,107 to 1,937,360 participants (Table 2).

Table 2 Summary of studies (datasets) included in the scoping review

Dataset	Country	Author	Year	Study population (N)	Aim	Comparison[1]
MESA	USA	Ambale-Venkatesh et al.(82)	2017	Adults aged 44-84 years from 2000 to 2002, without CVD, had magnetic resonance imaging N=4884	To investigate whether sphericity volume index, an indicator of left ventricular remodelling, predicts CVD	Characteristics of participants by incident event (CHD, CVD, HF, AF)
		Charry et al.(83)	2022	Adults aged 45-84 years from 2000 to 2002, assessed by ultrasound without CVD, SBP<180mm Hg N=5499	To investigate whether the total brachial artery reactivity is associated with the incident HF	No
		Steffen et al.(84)	2018	Adult aged 45-84 years from 2000 to 2002, without CVD, without cancer, without major illness, without cognitive impairment N=6,809	To determine whether lipoprotein (a) -related risk of HF is similar across difference races	No
MESA+DHS	USA	de Lemos et al.(85)	2017	Adults aged 45-84 years from 2000 to 2002, without CVD, without missing data from MESA N=6621 Adults aged 30-65 years from 2000 to 2002, without CVD, without missing data from Dallas Heart Study (DHS) N=2202	To evaluate a multimodality risk prediction strategy to improve atherosclerotic CVD risk assessment	No
LRPP	USA	Khan et al.(78)	2021	Adults between the ages of 20 to 79 years and free of cardiovascular disease at baseline, being followed up at least 10 years, with data on self-reported smoking status from 9 population-based cohorts were included N=106,165	To calculate long-term rates of incident CVD (overall and by subtypes) in adults aged 20 to 79 years To estimate years lived with and without CVD, on average, by baseline smoking status.	No
		Khan et al.(79)	2022	White and Black adults aged 20 to 59, free of CVD, had complete baseline measurement of risk factors N=24,838	To derive 30-year HF risk equations.	No

Dataset	Country	Author	Year	Study population (N)	Aim	Comparison[1]
NMEDW	USA	Bavishi et al.(80)	2020	Adults aged 30 to 79 years from Jan,2005 to Dec, 2013 and had a clinic visit at an internal medicine or cardiology clinic during this period, without CVD, being followed at least 5 years N=31,256	To examine the predictive accuracy of the Pooled Cohort Equations to Prevent Heart Failure model	No
		Rethy et al.(81)	2020	Adults aged 30 to 80 years and had a clinic visit at an internal medicine or cardiology clinic from Jan 2005 to Dec 2013, without CVD, being followed at least 5 years, with baseline addresses in Illinois N=28,858	To measure the association between neighbourhood-level poverty and incident HF	No
VA	USA	Garfield et al.(89)	2015	Adults aged 50-80 years from 1999 and 2000, without CVD, without bipolar disorder or affective psychosis, regular user of Veteran Affair Health Care N=236,079	To investigate the association between anxiety, depression or their co-occurrence are associated with incident HF	No
		White et al.(90)	2016	Case: adults HIV +, without CVD Control:age-,sex-,race and geographic matched HIV- veterans, without CVD. Participants enrolled between 1998 to 2003 from the US Department of Veterans Affairs (VA) system N=81,427	To determine the association between HIV, major depressive disorder and incident HF among veterans from Veterans Aging Cohort Study	No
Framingham Heart	USA	Cooper et al.(86)	2021	Adults aged 35-98 without CVD, underwent a non-invasive assessment of central hemodynamic, with laboratory or covariate data N=4700	To investigate whether intrinsic frequencies of carotid pressure waveforms are associated with incident heart failure	No
CARDIA	USA	Nwabuo et al.(87)	2019	Adults aged 18-30 years from 1985-86, without CVD, with 30 years of follow up, with echocardiography examination from 1990-1991(baseline visit) (baseline age 23-35) N=4107	To evaluate the utility of left ventricular global function index for incident HF and CVD	Characteristic of patients by CVD events (HF, Hard CVD and all CVD)
ARIC	USA	Ndumele et al.(88)	2016	Adults aged 45-64 years from 1987 to 1989 (baseline visit), without CVD, BMI≥18.5, Black or White N=13,730	To investigate the association between obesity and incident HF, CHD and stroke	No

Dataset	Country	Author	Year	Study population (N)	Aim	Comparison[1]
CALIBER	England	George et al.(91)	2015	Adults aged ≥30 years between Jan 1997 and March 2010, free of diagnosed CVD, had been followed up for at least 1 year N=1,937,360	To find out the relative frequency of different CVDs as they affect women and men in contemporary practice	No
		Shah et al.(92)	2015	Adults aged ≥30 years between Jan 1, 1998, to March 25,2010, free of diagnosed CVD, had been followed up for at least 1 year, no record of pregnancy within 6 months of study entry N= 1,921,260	To investigate and compare associations between type 2 diabetes and future risk of 12 of the most common initial cardiovascular presentations in men and women	No
UK-biobank	UK (England, Scotland or Wales)	Welsh et al.(94)	2019	Adults aged 40-69 from April 2007 and Dec 2010, with data on BP, without CVD, treated hypertension or diabetes mellitus N=322,624	To examine the relationship between sodium excretion and blood pressure in subjects without CVD	No
SMC	Swedish	Rautiainen et al.(93)	2015	Women aged 49-83 years in 1997 without cancer, CVD and no reporting extreme total energy intake N=34,319	To examine the association between fruits and vegetables intake and incidence of HF	No
Rotterdam	Netherlands	Leening et al.(95)	2014	Adults aged ≥55 years from 1989 to 1993 and 2000 to 2001, had no history of CVD events, had assessment of cardiovascular risk factors at baseline, and had available follow up data. N=8419	To evaluate differences in first manifestations of cardiovascular disease between men and women in a competing risks framework.	No
JMDC	Japan	Fukui et al.(96)	2021	Adults aged ≥20, enrolled in the JMDC Claims Database between Jan 2005 and April 2020, without CVD, with data on proteinuria and eGFR, with complete data on variables N=1,021,943	To compare whether adults with trace and positive proteinuria are at high risk for incident HF than those with negative proteinuria	No
		Matsuoka et al.(97)	2022	Adults aged ≥20, enrolled in the JMDC Claims Database between Jan 2005 and April 2020, without CVD, with available data on retinoscopy, with complete data on variables N=319,501	To examine the association between retinal atherosclerosis and incident HF	No

Dataset	Country	Author	Year	Study population (N)	Aim	Comparison[1]
NHIS-NSC	Korean	Kim et al.(98)	2020	Adults aged 30-84 years in 2007, underwent the national health screening for 2005-2007, without CVD, complete information for address and all covariates N=196,167	To examine the association between long-term exposure to particulate matter air pollution and CVD	No

Note: ARIC study =Atherosclerosis Risk in Communities, AF= atrial fibrillation, BMI=body mass index, BP= Blood pressure, CALIBER= CArdiovascular research using LInked Bespoke studies and Electronic Health Records, CARDIA study=Coronary Artery Risk Development in Young Adults, CHA =the Chicago Heart Association Detection Project in Industry Study, CHD= coronary heart disease, CHS =the Cardiovascular Health Study, CPRD=Clinical Practice Research Database, CVD=cardiovascular disease, eGFR= estimated glomerular filtration rate, FHS =Framingham Heart Study, FOF =Framingham Offspring Cohort, HF=heart failure, HIV= human immunodeficiency virus, ICD=International Classification of Disease, JMDC=Japan Medical Data Centre Claims Database, Kaiser old =the Kaiser Permanente Study of the Oldest Old, LRPP=the lifetime risk pooling project dataset, MESA =Multi-Ethnic Study of Atherosclerosis, NHANES I EF =the National Health and Nutrition Examination Survey I Epidemiologic Follow-Up, NHIS-NSC =Korean National Health Insurance Service-National Sample Cohort, NMEDW =Northwestern Medicine Enterprise Data Warehouse, RS= Rotterdam Study, SBP=systolic blood pressure, SMC=Swedish Mammography Cohort, VA=Veterans Affairs, [1] Comparison of baseline characteristics between HF and other outcome group

Table 3 Summary of definitions included in the results of scoping review

Dataset	Definition of HF	Definition of the baseline characteristics	Data source	Recruitment
MESA (81,82,83)	Medical records review :hospitalisations, (cardiovascular outpatient diagnoses) and death certificates Telephone interviewer call to inquire 6-9 months (self-report)	Self-report: demographic data, smoking, use of medication and other characteristics Physical examination measured at the study clinic Medical status including hypertension, diabetes based on self-report combined with physical examinations or laboratory tests	Medical records, death certifications, autopsy reports, interviews	Equal number of men and women were recruited from six targeted communities Passive recruitment: random digit dialling & active recruitment: mailing and telephone contact to households in targeted areas. Eligible information is collected so that all eligible persons can be identified from the contacted households.
MESA+DHS (85)	MESA: adjudicated DHS: adjudicated; survey done through phone call (annually)medical records-from hospital admissions using the Dallas–Fort Worth Hospital Council Data Initiative Database adjudicated by blinded end point committees	MESA: Self-report; demographic data, smoking, use of medication and other characteristics Physical examination measured at the study clinic DHS: self-report on demographic data, medical history and others Physical assessments including BP, heart rate, weight and others conducted by trained interviewers	Medical records, death certifications, autopsy reports, interviews	MESA: mentioned above DHS: The sampling frame was based on the US Postal Service delivery sequence file. Random samples were selected from 10 geographic strata. Eligible patients who were residents in Dallas County were then selected and contacted for an interview.
LRPP (77,78)	Kaiser old:Chart review & ICD-8&9 CHA:ICD-8&9 NHAES I EF:ICD-9 CHS: Adjudicated; clinic visits and surveillance calls and records were subsequently obtained (medical records reviewed by the CHS event subcommittee)	Self-report: demographic characteristics, diagnosis of diabetes and use of diabetes/ hypertensive medications Trained clinical staff conduct: physical examination (bp, weight, height)	Lifetime risk pooling project dataset	ARIC study: Area sampling and sampling from listings including a list of persons with driver's licenses, state identification cards or voter registration cards among residents of four geographically defined communities in the United States. CARDIA study : active recruitment through phone call or door-to-door invitation

Dataset	Definition of HF	Definition of the baseline characteristics	Data source	Recruitment
LRPP (77,78) (cont.)	ARIC: Adjudicated; phone contact annually & hospital discharges with cardiovascular diagnoses & death certificate Hospitalization discharge diagnoses were reviewed and considered eligible for validation as a HF event based on specific diagnoses codes. CARDIA: Adjudicated; 4 All participants were contacted annually by telephone and during scheduled study examinations to report interim hospitalizations. MESA: Adjudicated; Medical records review :hospitalisations, (cardiovascular outpatient diagnoses) and death certificates Telephone interviewer call to inquire 6-9 months (self-report) FHS: Adjudicated; medical records review: hospital adjudicated by 3 physician investigators FOF: Adjudicated; medical records review: hospital adjudicated by 3 physician investigators			MESA : active recruitment through telephone or mail aged 45-84 adults from 6 regions of USA CHS : community sampled from Medicare eligibility lists the Health Care Financing Administration (HCFA) Kaiser old: active recruitment to elderly who had gone through multiphasic health check-up exam; adults were from member of Northern California Kaiser Permanante Medical Care Program/ from KPMCP medical centres CHA : employees worked in Chicago area (firm) were recruited NHANES I EF : participants who completed a medical examination for NHAES I which used probability sample across counties in USA were recruited FHS: used a listing of all residents from a local census, active recruitment through community support FOF:Used records from the FHS to actively recruit FHS' eligible children

Dataset	Definition of HF	Definition of the baseline characteristics	Data source	Recruitment
NMEDW (79,80)	One inpatient ICD-10 & ICD-9 or two outpatient codes (ICD-9: 402.x1; 404.x1; 404.x3; 428.x ICD-10: I09.81; I11.0; I13.0; I50.x)	Clinical data collected at the index outpatient encounter Laboratory data from outpatient encounter: glucose, cholesterol, HDL Diabetes mellitus, hypertension status assessed by ICD	Northwestern Medicine Enterprise Data Warehouse	Participants were Illinois residents recruited from the NMEDW which contains data of patients who consented with data sharing and are served by Northwestern Medicine (NM)-affiliated hospitals.
VA (88,89)	From Inpatient and outpatient records: ICD-9-CM codes (428.xx, 429.3, 402.11, 402.91, 425.x)	VA administrative electronic records: sociodemographic data ICD-9-CM code: other CVD risk variables including smoking history, hypertension, type 2 diabetes, obesity, and smoking status	VHA datasets: inpatient and outpatient diagnoses, current procedural terminology (CPT) codes, pharmacy benefits management (PBM) records and vital status	Participants who use Veterans Health Administration (VHA) nationalized healthcare system and hence their data of all health-related encounters in the VHA are stored by the VHA national medical care data sets
Framingham Heart (86)	Medical records review: adjudicated by 3 physician investigators	Self-report: demographic data, smoking, use of medication and other characteristics Physical examination & laboratory test: height, weight, heart rate, BP, cholesterol, glucose measured at the study clinic Medical status such as diabetes based on self-report and laboratory test	Medical records, interviews	FHS (Framingham Heart Study): used a listing of all residents from a local census, active recruitment through community support 1999-2001 FOF (Framingham Offspring Cohort):Used records from the FHS to actively recruit FHS' eligible children 1998-2001 The Third Generation Cohort: children of Offspring Cohort participants were recruited actively through invitation letters 2002-2005

Dataset	Definition of HF	Definition of the baseline characteristics	Data source	Recruitment
CARDIA (87)	Hospital medical records and deaths review: adjudicated by committee members	Self-report: Alcohol use, tobacco use, antihypertensive medication use, and physical activity Physical examination: height, weight and BP Fasting glucose and medical status such as diabetics based on self-report and laboratory test	Medical records, interviews	The sample which could represent the population of black and white aged 18-30 is obtained in four urban areas in the USA. Targeted subjects were actively contacted through telephone and where phone contact was not allowed, subjects were contacted by door-to-door recruiters.
ARIC (88)	Discharge codes from hospitalizations: ICD-9 Death certificates: ICD-9 & ICD-10 (ICD-9: 428 ICD-10 : I50) 2005 onward hospital medical records and deaths adjudicated by expert panel	Self-report: medical history, physical activity, smoking status, alcohol consumption and other CVD risk factors Physical examination: weight, height, BP (not mentioned measured by whom) Medical status: diabetes measured by self-report or laboratory test	Reports of physical exam, interviews, discharge codes and death certificates	Participants were recruited from 4 US population centres. Recruitment methods involve area sampling, sampling based on listings. Once households were selected, residents were then targeted (didn't mention how to invite them).
CALIBER(90,91)	Primary care: the Read clinical coding scheme (G58..00) Secondary care: ICD-10 (I50, I11.0, I13.0 and I13.2) Death: ICD-10 (I50, I11.0, I13.0 and I13.2)	Primary care: the Read clinical coding scheme (Validity of Risk Factor and Disease Measurements in EHRs)	From electronic health records (Clinical Practice Research Database (CPRD) the Myocardial Ischaemia National Audit Project (MINAP), Hospital Episodes Statistics (HES) and the Office for National Statistics (ONS))	Participants who agreed with data sharing and registered in the English CPRD practices that participating the CALIBER program

Dataset	Definition of HF	Definition of the baseline characteristics	Data source	Recruitment
UK-biobank (94)	ICD-10 codes (I50)	Self-reported through questionnaire and interviews at assessment centres: socioeconomic characteristics, smoking status, medical history physical and functional measures at assessment centres: BP, weight	UK-biobank dataset	Participants were recruited based on their national health service (NHS) records (public funded care) which were used to identify that they were in the right age group and the recruitment relied on the inviting letters. With individual consent, their health-related records were then passed on to UK biobank through linkage to different datasets.
SMC (93)	ICD-10 codes (I50 and I11.0) Primary or secondary diagnosis diagnosis	Self-reported through questionnaire about lifestyle, clinical and dietary factors, smoking, alcohol consumption, educational level, hormone replacement therapy use, aspirin use, family history of myocardial infarction, history of hypertension and hypercholesterolaemia, and dietary supplement use was collected through self-report.	National Patient Registry, the Cause of Death Registry	Women born between 1914 and 1948, residing in Uppsala and Vastmanland counties in central Sweden were recruited by receiving an invitation letter and questionnaire.
Rotterdam (95)	Individual chart review: the combination of typical signs and symptoms	Participants self-report: questionnaire from home interview conducted by trained non-medical interviewers: medical history, health status, medication use. Physical examinations performed by physicians at the research centre Medical status-diabetes based on self-report or laboratory test	The automated follow-up system including ICPC codes, National Medical Registry (ICD code) and medical records	Participants living in the well-defined Ommoord district in the city of Rotterdam in the Netherlands invited by a letter
JMDC (95.96)	ICD-10 codes hospital claims records (I500, I501, I509, and I110)	Self-report: smoking and alcohol consumption JMDC database: health check-up results including weight, height, bp, diabetes mellitus, dyslipidemia, and prior medical history	JMDC database: medical and pharmacy claim records, annual health check-up data	Participants are those who used the universal health insurance service provided by the Japanese government and registered in the Japan Medical Data Centre (JMDC) Claims Database

Dataset	Definition of HF	Definition of the baseline characteristics	Data source	Recruitment
NHIS-NSC (97)	ICD-10 codes (I50) Primary or secondary diagnosis	Insurance eligibility database: Socio-economic characteristics General health examinations database: lifestyles, major health examination results	National Health Insurance Database	Participants served by the universal National Health Insurance (NHI) in South Korea and recruited for the National Health Insurance Service-National Sample Cohort (NHIS-NSC 2.0) based on their data in the National Health Insurance Database (NHID) are recruited if they also underwent the national health screening for 2005-2007.

Note: ARIC study =Atherosclerosis Risk in Communities, BP=blood pressure, CALIBER= CArdiovascular research using LInked Bespoke studies and Electronic Health Records, CARDIA study=Coronary Artery Risk Development in Young Adults, CHA =the Chicago Heart Association Detection Project in Industry Study, CHS =the Cardiovascular Health Study, CPRD=Clinical Practice Research Database, EHR=Electronic Health Record, FHS =Framingham Heart Study, FOF =Framingham Offspring Cohort, HDL=high density lipoprotein, ICD=International Classification of Disease, JMDC=Japan Medical Data Centre Claims Database, Kaiser old =the Kaiser Permanente Study of the Oldest Old, LRPP=the lifetime risk pooling project dataset, MESA =Multi-Ethnic Study of Atherosclerosis, NHANES I EF =the National Health and Nutrition Examination Survey I Epidemiologic Follow-Up, NHIS-NSC =Korean National Health Insurance Service-National Sample Cohort, NMEDW =Northwestern Medicine Enterprise Data Warehouse, RS= Rotterdam Study, SMC=Swedish Mammography Cohort, VA=Veterans Affairs

The most common method of recruitment used by eight of the datasets was a recruiting study population from well-defined geographical areas through listings, such as household listings, local census listings, a US Postal Service delivery sequence file or lists of driver's licenses or state identification cards (82–88)(89,90) (Table 3). Five studies from two datasets recruited their study population from primary care including general practices and outpatient settings for preventive care (80,81,91,92,94) (Table 3). Four datasets included their study population from the national health registry system. Among these, three invited their study population from their universal national health service (96–98). One recruited their participants from the Veterans Health Administration nationalised healthcare system (89,90) (Table 3).

The time period for starting the recruitment of the study population was around 2000s for most datasets (n=9) (79,80,82–86,88–93,97) (Table 3). The time period for one dataset was as early as 1987-1989 (88)and another two datasets had their time period around the 1990s (87,95) (Table 3). The most recent period was between 2005-2020 for one dataset (96,97). Two studies did not report their time periods (78,79). The focus of one dataset that accounted for the age range of the source population considered people aged 20-35 (87) while one dataset included participants aged 20-59 (78) and one dataset had participants aged ≥20 (96,97) (Table 3). Population aged ≥30 were studied by four datasets (80,81,86,91,92,98). Participants aged 40-69 were studied by one dataset (94) while participants aged 45-64 were studied by one dataset(88). There were three datasets focused on people aged ≥45 (82–84,86,93) (Table 3). In terms of age range at 50-80, it was included by one dataset (89). Only one dataset included people aged≥55(95). Regarding the sex of the source population, while most studies involved both female participants and male participants, one study exclusively focused on women (93)and one study was mainly comprised of men (98%)(89) (Table 3).

3.5.3 Definition of heart failure and methods for data collection

In this scoping review, a large number of datasets defined HF utilising the World Health Organization's International Classification of Disease code (ICD) including ICD-8, ICD-9 and ICD-10 (n=9) (77–80,87–93,95,97) and three of them identified hospitalisation with HF as either primary or secondary diagnosis (92,95,97)while others did not report it (Table 3). Among studies which only used ICD codes to define HF (n=9)(79,80,88,89,92,93,95,96,97), one dataset was based on both inpatient and outpatient records (80,81) and the rest were solely based on inpatient records (Table 3). Among the datasets that did not only use ICD codes (n=3), besides using hospital discharge code, two datasets defined HF based on the review of hospital medical records (78,79) and one dataset included the primary care codes (91,92) (Table 3). HF was mainly defined by medical records review in the rest of the five datasets (82–86,94), in which HF was adjudicated based on hospital charts review (n=4) or adjudicated based on both general practitioner reports and hospital charts (n=1) (Table 3).

In terms of the codes used to define HF, one dataset used READ codes G58..00 to define HF (91,92). The most common ICD-9 codes used to define HF were 428 (80,81,88–90) while the most common ICD-10 codes used to define HF were I50 (80,81,88,91–94,96–98) (Tabel 3). Other ICD-9 codes used were 429.3, 402.11, 402.91 and 425.x by one dataset (89,90) and 402.x1, 404.x1 and 404.x3 by another (80,81). In terms of ICD-10 codes, other ICD-10 codes used were I13.0, I13.2 by one dataset (91,92) and I09.81 and I13.0 by another (80,81) (Table 3).

For datasets which used codes to ascertain HF, the relevant data was collected from a specific dataset, such as National Health Insurance Database, UK-biobank dataset and JMDC database which have linkages to administrative data or healthcare records (n=8)(77–80,88–91,93,95,97) or directly from the relevant registries (n=1)(93) (Table 3). For datasets which relied on medical records review to ascertain HF, the relevant data was firstly collected during a regular telephone interview or a routine clinic visit in three and the other two involved an electronic health record search through the linkage of a specific database to medical records (85,95) (Table 3).

3.5.4 Definition of baseline characteristics

From Table 3, it can be noticed that most datasets defined socio-demographic characteristics through patient self-report (n=11)(77–80,82–85,87,92–95), while the rest of the studies defined

them based on databases including administrative data and/or electronic health records (n=3)(89–92,98). Regarding risk factors, such as medication use, medical status including hypertension and diabetes, lifestyle factors including smoking status and alcohol consumption, eight datasets identified them through patient self-report (81-87,92,94) among which five datasets identified medical status from either self-report in terms of using the relevant medication or physical examinations and laboratory tests which were specifically conducted for the study. Three datasets defined these risk factors through databases (89–92,98) and three datasets were based on both databases and patient self-report especially for lifestyle factors (80,81,96,97). In terms of anthropometric measurements, BP, cholesterol and glucose which was specifically conducted for the study, a great number of datasets defined them through physical examination and lab tests (n=9)(78–81,83–88,94,95,99), four were based on databases (89–92,96–98). and a single study did not report it (93).

3.5.5 Comparison of baseline characteristics according to outcomes

Only two studies that focus on people who had no previous history of CVD including HF provided the description of the baseline characteristics of patients according to their outcomes (82,87) (Table 4). In Ambale-Venkatesh et al. with a median follow up time 10.2 years, it was found that compared to patients whose first CVD event was CHD, patients with HF as their first CVD event tended to be older, had higher values of SBP, BMI, HDL and a higher percentage for hypertension medication use, and having diabetes and had a higher Framingham CVD risk(82) (Table 4). In the study by Nwabuo et al. where the median follow-up was 24.9 years, while comparing patients with HF to patients whose first CVD was hard CVD including HF, a younger age and higher values of SBP, DBP and HDL were noticed in patients with HF (87) (Table 4).

Table 4 Summary of baseline characteristics of patients according to their outcome in Ambale-Venkatesh et al's study and Nwabuo et al's study

Ambale-Venkatesh et al(82)		Outcome		
	Baseline charactertics	HF (n=142)	CHD (n=302)	CVD (n=421)
	Mean age, years (mean,SD)	68 ±9	66±9	67±9
	Gender (% males)	63.5	69.2	63.1
	Race (Ca, Ch, AA, Hi)	43/5/32/19	47/8/25/20	46/8/25/21
	BMI (kg/m2) (mean,SD)	28.6 ±4.8	28.3 ±4.9	28.4±4.8
	Smoking status (current/former) (%)	17/42	18/42	18/39
	Systolic blood pressure (mm Hg)(mean,SD)	138±23	133±22	135±23
	Hypertension medication (%)	59	51	51
	Diabetes (%)	28	21	20
	Cholesterol (mg/dL)(mean,SD)	190±35	196±37	195±36
	HDL(mg/dL)(mean,SD)	50±14	47±14	47±13
	ACE inhibitor (%)	26.4	18.2	17.9
	10-year Framingham CVD risk (Circ 2008/SD)	22.3±8.3	21.0±8.8	20.9±8.7
Nwabuo et al(87)		Outcome		
	Baseline characteristics	Heart failure (N=59)	Hard CVD (N=185)	All CVD (N=207)
	Mean age, year (SD)	30.7 ±3.8	31.09 ±3.6	31.2±3.5
	Gender, n(% men)	61.0	62.2	61.8
	Race, Black, n (%)	49 (83.1)	120 (64.9)	127 (61.4)
	SBP (mmHg), mean (SD)	116.3 ±15.2	114.8 ±15.0	114.1±14.7
	DBP (mmHg), mean (SD)	76.7 ±12.6	74.8±12.1	74.3±12.0
	Diabetes, n (%)	1 (1.7)	12 (6.5)	13 (6.3)
	HDL (mg/dL), mean (SD)	51.7±14.6	49.1±14.4	48.7±14.3
	Current smoker, n (%)	26 (44.1)	92 (50.3)	98 (47.8)
	Hypertension medication n (%)	4 (6.8)	13 (7)	14 (6.8)

Note: AA=African American, ACE=angiotensin-converting-enzyme inhibitor, BMI=body mass index, Ca=Caucasian, Ch=Chinese American, CHD=coronary heart disease, CVD=cardiovascular disease, DBP=diastolic blood pressure, HDL=high-density lipoprotein, HF=heart failure, Hi=Hispanic, SBP=systolic blood pressure, SD=standard deviation

3.6 Discussion

In this scoping review, 21 articles that studied patients with HF as their first CVD events and demonstrated in detail about the way they define HF and the baseline characteristics of the patients were identified. It is found that ICD codes and medical chart review were used most often in studies to define HF and the information was most often entered into electronic databases. Also, in terms of defining the baseline characteristics of patients, self-report information, EHR, administrative data and clinical assessments were used. Only two studies provided the comparison of the baseline characteristics of HF patients and other CVD patients and there were a number other differences that were all detected. Patients whose first CVD

event was due to HF tended to have higher values of SBP, DBP, HDL and BMI, use hypertension medication more frequently and had diabetes in comparison with patients whose first CVD event was due to other CVD outcomes.

Most of the included studies reported that their eligible population could be well representative of the source population and some of them could even represent the national population in terms of age, sex and ethnicity. However, as the manifestations of HF differ by race, and the ethnicities of study cohorts varied, these study findings might not be able to generalise to other ethnic groups, such as the Māori and Pacific people (95). Considering the changes in the prevalence of CVD risk factors which has been observed over the last few decades and the progression in medical interventions for preventing CVD, it is possible that the study results were subject to birth cohort effect (101). This means that even with similar age ranges, the cohorts that were recruited from different time periods might have different characteristics and outcomes (95,102).

This scoping review also highlights the need to consider the choice of source population which is crucial to the external validity of the studies while interpreting results (103). The included studies were based on different settings ranging from community-based sources, primary care, speciality clinic (infectious) and national health insurance service. Cohorts recruited from different sources can have different baseline characteristics and health outcomes. For example, community-based sources relied on the responses from volunteers that might introduce a "healthy volunteer effect", which leads to the underestimation of the actual incidence of most of the diseases in a short time after baseline (95,96). Also, considering reasons, such as financial or geographic barriers or religious beliefs which can have an impact on one's decision to enter the healthcare system, the healthcare system based cohorts' baseline characteristics, such as socio-demographic factors might differ from that of community-based cohorts (104). The level of disease severity could determine the entry of the primary care or the speciality clinic to a certain extent and thus imply the possibility of a different level of underlying health conditions (104,105). Therefore, even for samples which were selected from the healthcare system, the cohort based on primary care might be different from the cohort based on speciality clinic (104,105).

This scoping review finds that different methods were used to define HF. The use of ICD codes linked to hospitalisation or specific databases is a cost-saving and efficient approach to identify

and evaluate a large number of HF patients for long term studies in comparison to methods, such as medical records review (74). Although McCormick et al. showed that true HF cases could be highly predicted by administrative databases, a quarter of the non-trivial HF cases were not captured (74). The diagnosis obtained from the medical chart review is considered to be more accurate, this is the reason it chosen as the "gold standard" reference diagnosis while measuring the validity of HF diagnoses in administrative databases (74).

For the included studies which used ICD codes and reported the diagnosis used, it was common to include both primary and secondary diagnoses to detect HF. A systematic review which aimed to evaluate the validity of algorithms found that compared to studies which only relied on the primary diagnosis of HF, the positive predict values (PPVs) were slightly lower in studies which used diagnoses in any position (106). The algorithm which only uses primary diagnosis of HF might have a higher PPV, which meet the requirement for studies that are interest in the new occurrence of HF (106). However, with the decreasing of HF in the primary position and the increasing of HF in secondary positions, in order to better balance specificity and sensitivity in terms of capturing HF cases, it is crucial to include diagnoses in any diagnostic position, which might also enable the comparability of the data between studies (74).

While most studies defined HF based on hospitalisation data alone, some studies used the combination of primary and secondary care data, such as outpatient visits in the US and GP visits in the UK and Rotterdam. The variation of HF manifestation leads to the different health-seeking behaviour of patients. For example, patients with early stages of HF would be more likely to visit their GPs and have their symptoms managed at the primary healthcare (107). In the case of the CALIBER studies, 22% of HF cases were recorded in the primary care only (108). Therefore, if HF cases were ascertained mainly based on hospitalisation data, mild HF cases might be missed. Nevertheless, the balance of specificity and sensitivity in terms of diagnosing HF in the primary care should be considered. With the use of an expert panel, a UK study estimated the accuracy of HF diagnosis in the primary care and showed the possibility that a third of patients might be incorrectly labelled with a diagnosis of HF in primary care (107,109). A survey showed that compared to cardiologists, general practitioners had much less confidence in diagnosing HF, especially in the situation where the specific HF symptoms were lacking, which might explain the increase in the proportion of HF patients whose first diagnosis happened in the hospitals from 50% in 2003 to almost 80% in 2013 (109)(107,110). In addition, the limitation of available time, the limitation of access to investigations and the

lack of confidence in the interpretation of the results might all have an impact on the accuracy of HF diagnosis in the primary care (107).

Moreover, Saczynski et al. demonstrated that studies which used the combination of outpatient encounters and hospital discharge diagnoses to define HF were more likely to have lower PPVs compared to studies which only used hospital discharge diagnoses (106). Nevertheless, it is important to be aware that PPV is determined by how prevalent a condition is in the study population, which suggests the possibility that the higher PPV might be contributed to by the higher baseline risk of HF in the study population. The differences in the baseline characteristics of HF outpatients and inpatients was noticed in the study by Ferreira et al. and in comparison to HF inpatients, the HF outpatients had fewer co-morbidities and lower event rates (111). Based on the risk score developed by this study, it can be seen that 53% of outpatients were categorised as in the low-risk group and 19% were in the high-risk category while 37% of inpatients were categorised as low-risk and 33% were in the high-risk category (111). These differences show that compared to the study population in studies which defined HF based on the outpatient records alone or the combination of outpatients and inpatients records, patients in studies which defined HF based exclusively on hospitalisation data are more likely to have the same degree of severity due to the fact that there is a certain threshold for hospitalisation (107,111). These differences might affect the generalisability of the research findings to the HF population.

In the process of case ascertainment, for medical chart review it was initiated by self-report from participants, so events might be missed due to reasons, such as the loss of contact with patients or study personnel not being able to obtain medical charts (112). For example, a study which compared administrative data and physician adjudication for identifying outcome events demonstrated the situation where the diagnosis code was recorded in the administrative data but no relevant hospitalisation report was provided by the participants due to misunderstanding the purpose for that admission (113). This will less be the case for approaches which obtain data from the specific datasets. With the linkage between different healthcare databases, diagnosis codes from hospital can be easily tracked and recorded.

This review also finds that the methods used to define the baseline characteristics varied and the comparability of information of patients' baseline characteristics may vary across studies due to the different methods. Research grade data which are based on physical examinations

and laboratory tests are considered to be more accurate relative to self-report information, electronic health records (EHR) or administrative data due to the strict processes of data collection (114). As a result, research grade data is used as a "gold standard" while comparing the accuracy of other methods (115).

Self-report measures were most frequently used due to their cost-effectiveness and time efficiency in comparison to physical examinations and laboratory tests (116). However, it is argued that self-reported data is less accurate and reliable as misclassifications are likely to be introduced. Misclassification can be produced by reporting bias including social desirability bias which is commonly associated with asking sensitive questions, such as smoking status and alcohol consumption and recall bias which is associated with a recall error and it can contribute to either an underestimation or an overestimation of the true effect (117,118). Also, the comparability of self-report information can be reduced by diagnosis bias and diagnosis avoidance for example diabetic status not having been successfully detected previously in the participants (119). A systematic review which focused on investigating the accuracy of self-reported information including health behaviours and risk factors associated to cardiovascular disease in the general population questioned the method of relying exclusively on self-report information (115). It was found that while comparing the prevalence of health behaviours and risk factors collected from the self-report data and from the corresponding gold standard data, there were significant differences estimated between them (115). Another article that validated the self-report data of cardiovascular risk factors among high risk population found that out of three risk factors measured, half of the population reported at least one of the risk factors inaccurately and a low sensitivity related to self-report was estimated (120). Nevertheless, in the study by Rautiainen et al. while the degree of agreement between the self-reported information for weight and height and previously measured values was validated high, the accuracy of other risk factors of interest was not investigated (93).

EHR and administrative data were also commonly used to define the baseline characteristics of patients. The use of this data can contribute to the improvement of efficiency and the reduction of cost for the research and the quantity and real-world nature of the data is also the reason it is used (114,121). However, it is concerned that this data might be less accurate than prospective clinical assessments, due to the inherent limitations, such as the fact that they it is not collected for research uses but assisting individual physicians in diagnosing, treating and monitoring health conditions or for administrative or billing purposes (114,121). For example,

the substantial amount of missing data which is often a common issue in databases can cause misclassification (114). Nevertheless, Bavish et al. and Rethy et al. demonstrated that their EHR data had good sensitivity and specificity (80)(81). By comparing EHR data to the individual level data from the MESA study which defined risk factors based on in-person clinical assessments, except for BP measurements, good agreement between BMI measurement, sex, race and age was found. Also, with the use of ICD-9 and clinical data from the EHR database, good sensitivity and specificity of hypertension, obesity and diabetes were detected (122). Fort et al. also noticed a good correlation for BP, BMI, gender and race between EHR data from a single institution and data from a community-based study (114). Similarly, in CALIBER study, taking physicians questionnaires as a gold standard, algorithms for risk factors including smoking and obesity tested valid (123). These underscore the accuracy and reliability of EHR and administrative data to a certain extent.

3.7 Limitation

This review has important limitations. To enable the feasibility of the review, searching was only conducted in one database, hence the adequate coverage cannot be guaranteed, which means that not all approaches that were used to identify HF and baseline characteristics might be included. Furthermore, this review chose to focus solely on studies that were interested in people who have HF as their first CVD event, so the findings may not be generalisable to other conditions.

3.8 Summary of scoping review and its implication for the quantitative analysis of this thesis

The variation of HF definition and baseline characteristics definition was reviewed. Within the 21 studies, it was found that ICD codes and medical chart review were used most often to define HF, while clinical assessments, self-report information, EHR and administrative data were the sources used to define baseline characteristics. This study explored the strengths and weaknesses of methods applied to define HF and the baseline characteristics and how they might affect the accuracy and thus the comparability of the data.

In the aspects of defining HF, while ICD codes are considered to be more cost-saving and efficient while comparing them to the medical chart review, the medical chart review is understood to be more accurate. While using ICD codes to define HF, although the PPVs were

slightly higher in studies which solely relied on the primary diagnosis of HF, including diagnosis in any position (primary and secondary diagnosis) might better balance specificity and sensitivity in terms of capturing HF cases. Using the combination of outpatient encounters and hospital diagnoses to define HF were likely to have lower PPVs compared to studies that only used hospital discharge diagnoses. In the aspects of defining baseline characteristics, self-report was frequently used due to its cost-effectiveness and time efficiency but it has been argued that it might not be as accurate or reliable as misclassifications are likely to be introduced. On the other hand, clinical assessment conducted by health professionals has shown reasonable accuracy and EHR and administrative data was also frequently used with the support of good sensitivity and specificity.

Considering that the aim of the quantitative analysis is to describe patients whose first CVD presentation was due to HF by comparing them to patients whose first CVD presentation was due to other CVD, a large number of the study population will be involved. As 95% of New Zealanders are enrolled in the primary health organisations, the primary care can be a suitable setting to recruit the cohort and due to the well representative of the source population, the external validity of this thesis is likely to be increased (103). Also, considering the large amount of study population that will be included, data from the coding system, such as ICD-10-AM can be a cost-saving and efficient approach to identify HF as well as serve as support for long term studies in comparison to methods, such as medical records review (74). With the awareness of the higher PPVs in studies which defined HF based only on hospital discharge diagnoses and health professionals' lack of confidence in diagnosing HF in primary settings, it is more appropriate to only include hospitalised patients while identifying HF cases (106) (107,110). In terms of the identification of the baseline characteristics, clinical assessment should be used due to its accuracy and EHR might also assist in providing some specific information, such as demographic data. The findings from the CALIBER database and MESA database will be compared to the findings of the quantitative analysis of this thesis in chapter 6 to demonstrate how variations in definition might have an impact on the findings.

4 Chapter 4. Method of Analysis of New Zealand data

The last chapter mapped the definition of HF and the baseline characteristics of the patients through a scoping review. In order to achieve the aim and objectives listed below, NZ data will be used. As the PREDICT electronic decision support programme was constructed for primary care use to assess and manage CVD risk and thus facilitated the recruitment of cohort. The PREDICT data will therefore be used for this quantitative analysis. This chapter outlines the study design. It explains PREDICT and discusses study the sample, key baseline characteristics, outcomes and statistical analysis. This chapter concludes by discussing the ethical issues.

4.1 Study design

This is a cohort study undertaken of people without CVD who had CVD risk assessment using the PREDICT electronic decision support programme in NZ. Data from participants' CVD risk assessment were linked using an encrypted National Health Identifier to data from regional and national health data collections. Specifically, data from patients who were assessed by the PREDICT from October 2004 and October 2018 were analysed.

The study was conducted to achieve the following aim and objectives.

4.1.1 Study aim and objectives

Aim

To compare the characteristics of people whose first CVD hospitalisation was due to HF with those presenting with other types of CVD in order to gain a better understanding of the differences in their characteristics and the sufficiency of CVD risk assessment for HF prevention.

Objectives.

1. To describe the characteristics of HF patients including demography, comorbidities, clinical characteristic and cardiometabolic medication
2. To compare the characteristics of patients who had HF as their first CVD event with those who had other atherosclerotic disease, haemorrhagic stroke or cardiac fatal event as their first CVD event
3. To estimate the proportion of patients who had HF as their first CVD event and had subsequent admissions associated with CHD

4.1.2 PREDICT

PREDICT is a web-based decision support tool for assessing and managing CVD risk and it was constructed for primary care use (53). The use of PREDICT to assess a patient's CVD risk is at the discretion of the general practitioners (GP) or practice nurse (124). **T**he enrolled patients in primary health organisation take up around 95% of New Zealanders and approximately 35%-40% of them are served by practices using PREDICT software, which are mostly located in the Auckland and Northland regions and composed of large urban and substantial rural populations. (53) According to the data, patients who were eligible for CVD risk assessment and had it completed in clinics using the PREDICT program were around 80 percent (1)**.**

When the PREDICT software is opened during a patient visit, it is auto-populated with the patients' clinical data from their medical record with any missing fields that are to be filled in by the clinicians, which increases the accuracy and the completeness of data collection (125)(126). After the online form has been completed, a risk score which is based on the NZ Primary Prevention Equations (explained in 2.7.5) (4), as recommended by the New Zealand Guidelines (explained in 2.7.5) (65) are calculated and evidence-based recommendations adapted for the patient's CVD profile is provided by PREDICT and other electronic decision support tools (53). In this way, general practice electronic health records (EHRs) integrates PREDICT, which in turn includes data collection into clinical workflow (53). The EHR and a secure off-site server (Enigma Solutions Ltd) keeps a copy of the patient's CVD risk profile which is encrypted and used for research(53). The design of PREDICT involved Enigma Publishing Limited, the Vascular Informatics using Epidemiology & the Web (VIEW) research team at the School of Population Health, and various healthcare organisations (65,125).

4.2 Study sample

The source, types and definition of all variables mentioned below are explained in the appendix 1 and appendix 2.

The PREDICT cohort with entry period between October 2004 and October 2018 was used in this study. This study population well represents New Zealand's diverse socioeconomic and ethnic groups (53).

In order to achieve the objective of describing the baseline characteristics of the PREDICT cohort, denominator A for this analysis was the all study population who were aged between 30 and 74 years and met the inclusion and exclusion criteria with identified ethnicity not Middle Eastern, Latin American and African(MELAA), other or unknown, not residing overseas, not having CKD or kidney transplantation, having records of smoking status and TC/HDL ratio and not having a previous CVD or HF history.

In order to achieve the objective that is to estimate the proportion of patients who had HF as their first CVD event and had subsequent admissions associated with CHD. Denominator B for this analysis will be restricted to all participants whose first presentation of CVD during follow up was for HF. Numerator B for this analysis will be restricted to participants who had subsequent admission due to CHD within one year due to CHD.

Patients aged 30-74 years are included for the aim of the study and this age range reflects that CVD below age 30 is rare, and the upper age recommended by the New Zealand CVD risk-management guidelines for a CVD risk assessment (127). In addition, the study population was divided into two age groups 55 years and above and under 55 years of age. The rationale for choosing 55 as the cut-off age for dividing the study population is because that 55 is in the middle between age 30 years and age 74 years and age 55 years is considered as a young age to start having CHD especially acute coronary syndrome (128). People whose history of CVD were defined in PREDICT and whose previous hospitalisation was coded for CHD, haemorrhagic or ischemic cerebrovascular stroke, TIA, PVD, or other CVD-related procedures were identified as having prior CVD events (appendix 2). These people were excluded due to the study aim that involves describing the characteristics of patients whose first presentation of CVD was for HF. Also, people with previous CVD history are not recommended to use the NZ Primary Prevention Equations as their risk management and lifestyle modification is more aggressive (4). If the linked national drug dispensing database showed the patients' dispensing of anti-anginal drugs before their index assessment, these patients were grouped as having prior CVD and were excluded (127). Due to the factor that loop diuretics are more commonly used for HF than other conditions in New Zealand, while having prior hospitalisation for heart failure was defined as prior HF, being dispensed at least three loop diuretics in the five years before undergoing the index assessment and/ or being dispensed metolazone in the last six

months before undergoing the index assessment were also defined as prior heart failure (65,127).

Patients who identified their ethnicity as Middle Eastern, Latin American, African or recorded as "other" or "unknown" were excluded (appendix 1), as it was difficult to combine these ethnic groups into one category due to their heterogeneous feature and the numbers were too few to separate them into meaningful subgroups (127). Patients who were not identified as having NZ residency were excluded. Patients with chronic kidney disease (CKD) demonstrated by nephropathy or estimated glomerular filtration rate<30 ml/min were excluded. The rationale for this exclusion was that patients with CKD were already known to have a very high CVD risk and individualised management was required (4). People with prior kidney transplantation or on dialysis were excluded for the same reason, being a risk-equivalent to having had CVD (4). Patients with missing data on the smoking status and Total cholesterol/HDL ratio were excluded. The laboratory measures came from the PREDICT and TestSafe and the out of range values of TC/HDL ratio were recorded as missing (TC/HDL ratio<1.08 OR >30.1; Total cholesterol<1.51 OR >35.5; HDL cholesterol<0.13 OR >5.1; LDL cholesterol<0.3 OR >11.5) (126).

4.3 Key baseline characteristics

For calculating 5-year CVD risk, the mandatory fields of the online CVD risk assessment forms are date of birth, sex, ethnicity, NZDep, smoking status, diabetes status, family history of premature CVD, history of atrial fibrillation, up to two measures of systolic blood pressure in mmHg, the ratio of total cholesterol to high density lipoprotein cholesterol concentrations (TC/HDL) and use of blood pressure lowering, antithrombotic drug or lipid-lowering drug (appendix 1) (4). These risk factors were investigated. The estimated glomerular filtration rate (eGFR) was also included as a risk factor, considering its association with the risk of having CVD (appendix 1)(129). Additional risk factors known to have an association with HF were also assessed, including history of valvular disease, history of cardiomyopathy, and implantation of a cardiac device (pacemaker, cardioverter defibrillator, or valve replacement) (appendix 1). (26).

4.4 Outcomes

The first cardiovascular event during follow up, after the index date, was the outcome of interest. This was defined as non-fatal (HF, CHD, Cevd, PVD, HS) or fatal. It could be identified from the NMDS and the Mortality Collection using the ICD-10-AM codes demonstrated in the appendix 2. Events were coded based on discharge diagnoses including both primary and secondary diagnosis in order to maximise sensitivity. With the knowledge that medical conditions are not mutually exclusive and therefore one patient can have multiple diagnoses, it was decided to prioritise CVD events where multiple CVD events occurred during a single admission to simplify the analysis. The order of prioritisation where multiple CVD events occurred during a single admission was: STEMI, NSTEMI, unspecified MI, unstable angina, other CHD, HF, Stoke, TIA and PVD. Therefore, if a first presentation for CVD included any type of coronary heart disease, this was prioritised ahead of HF during the same admission. The decision on which ICD-10-AM codes to include and how to prioritise different types of CVD which could occur in one admission were made in consultation with Associate Professor Katrina Poppe and Dr Vanessa Selak, in alignment with the coding practices of the VIEW programme.

4.5 Statistical analysis

Descriptive statistics were used to summarise the baseline characteristics of the PREDICT cohort. Categorical data were summarised as percentages and frequencies while continuous variables were summarised as means with standard deviations or medians with interquartile ranges.

The differences in baseline characteristics were investigated for people who had HF during follow up with people who had other CVD events including CHD, Cevd, PVD and HS and fatal events that were included as comparator groups. They were investigated by female and male groups due to the observed sex difference in CVD and HF(130). The proportion of patients who had HF as their first CVD event and had subsequent admissions associated with CHD were estimated as well.

The statistical significance of differences between men and women were tested with 2-sample t-test for continuous variables and chi-square independence test for categorical variable and

between multiple groups was determined using the analysis of variance for continuous variables and chi-square test for categorical variable.

All data analysis was performed using Stata 14.0 software, with the level of statistical significance set at p=0.05 (131).

4.6 Ethics approval

The PREDICT study was approved by the Northern Region Ethics Committee Y in 2003 (AKY/03/12/314) and there has been annual approval by the National Multi Region Ethics Committee since 2007 (MEC09/19/EXP). Consent from individual participants has not been required with a waiver granted by the ethics committee in this situation considering that the befits outweighed the harms. Also, the encrypted NHI instead of live NHI are used for research, which increases patient privacy while enabling data linkage.

4.7 Summary of chapter 4

This is a cohort study that has been undertaken of people without CVD who had CVD risk assessment using the PREDICT electronic decision support programme in NZ. Data from participants' CVD risk assessment were linked using an encrypted National Health Identifier to the data from regional and national health data collections. Specifically, data from patients who were assessed by PREDICT between October 2004 and October 2018 was analysed. Participants who developed a CVD event during follow up were identified from the NMDS and the Mortality Collection using the ICD-10-AM codes. The codes were classified according to the type of CVD event and their characteristics at the time of the CVD risk assessment were compared. Data management was performed for descriptive analysis. All data analysis was performed using Stata 14.0 software, with the level of statistical significance set at p=0.05. The statistical significance of differences between men and women was tested with 2-sample t-test for continuous variables and the chi-square independence test for categorical variable and between multiple groups was determined using the analysis of variance for continuous variables and the chi-square test for categorical variable. The following chapter will describe the results of the analysis.

5 Chapter 5. Results

This chapter presents the findings from the analysis of the PREDICT quantitative data. Patients who had HF as their first CVD event are described according to their demography, comorbidities, clinical characteristic and cardiometabolic medication. Patients who had HF as their first CVD event and those who had a different first CVD event are compared according to these characteristics. In order to assess the underlying CHD among patients who had HF as their first CVD event, subsequent admissions associated with CHD among the people who have HF as their first CVD event is also investigated.

5.1 Participants

The original PREDICT dataset included 563,346 New Zealanders aged 18 to 105 years of age whose CVD risk was first assessed in PREDICT between October 2004 and October 2018 (Figure 2). There were 36,032 people excluded as they were not between 30 and 74 years of age. Sequentially, 8,288 were then excluded as their ethnicity was Middle Eastern, Latin American, and African (MELAA) or not stated. 5,322 patients identified as not having NZ residency, 3,496 patients with nephropathy and 1,633 patients with renal dialysis/transplantation were also then excluded. The exclusion followed by three patients who had no record of smoking status and then 43,319 patients who did not have a record that met the study criteria. 11,889 patients had a history of HF, and 36,433 patients had a history of CVD, therefore they were not included. Finally, 6,110 patients estimated glomerular filtration rate (eGFR) lower than 30 ml/min and thus were excluded. Hence, after exclusions, a total of 410,821 participants were left in the analysis.

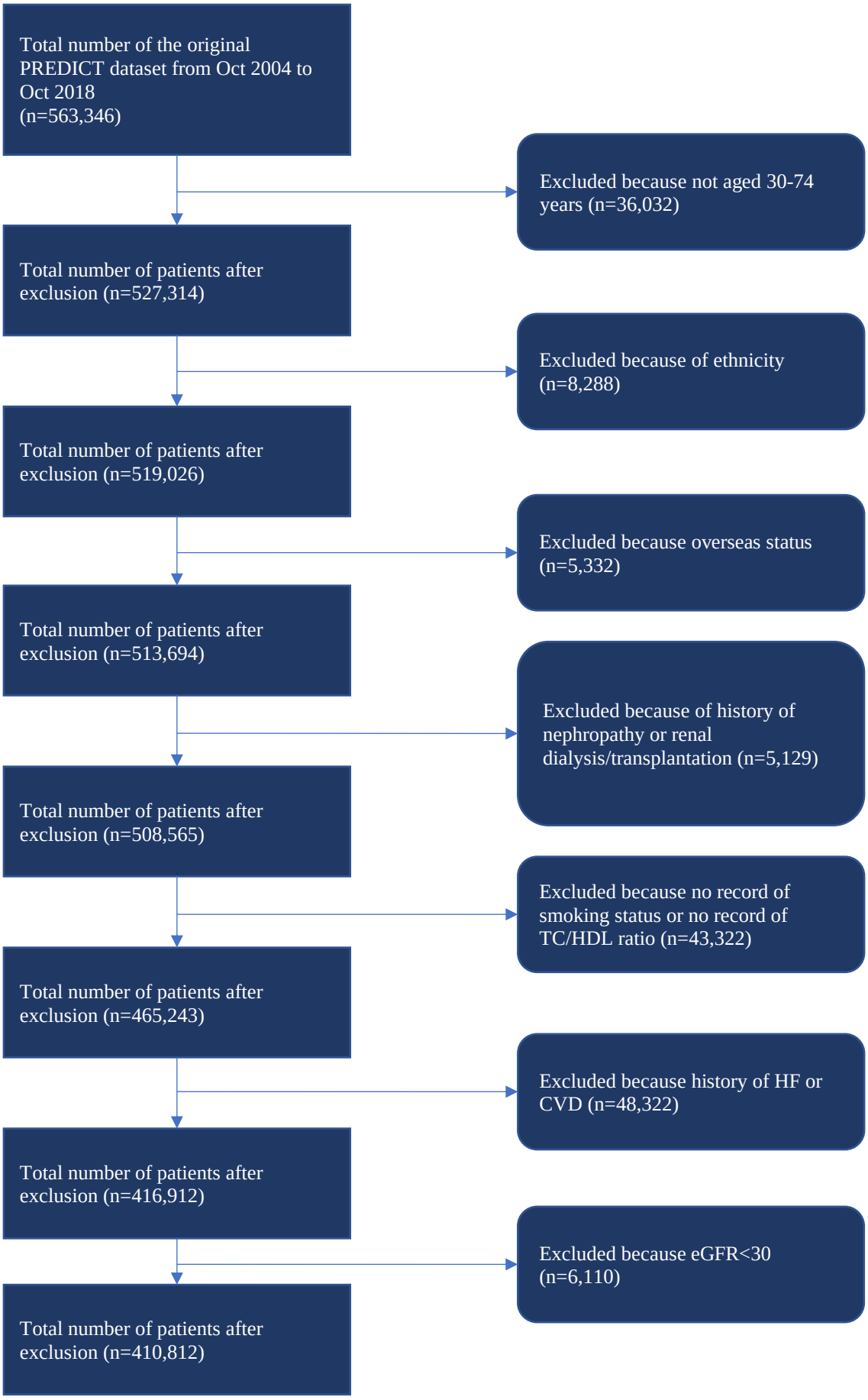

Figure 2 Cohort flow chart illustrating the inclusion and exclusion critria of participants in the study

5.2 Baseline characteristics

The baseline characteristics of the entire cohort are depicted in Table 6 by sex. The total number of the participants was 410,821 and men comprised the majority of the cohort (56.3%).

Table 5 Baseline characteristics of the entire cohort

		Women		**Men**		**Total**		**p-value***
Participants (percentage of total cohort)		179,435 (43.7)		231,386 (56.3)		410,821		
Mean age, years (SD)		55.7 (8.9)		51.3 (10.1)		53.2 (9.8)		<0.001
Prioritised self-identified ethnicity, n (%)								<0.001
European	≥55 years	72,144 (67.5)		57,452 (68.1)		129,596 (67.8)		
	<55years	22,204 (30.6)		67,902 (46.2)		90,106 (41.0)		
Māori	≥55years	7,756 (7.3)		6,467 (7.7)		14,233 (7.4)		
	<55years	17,046 (23.5)		22,359 (15.2)		39,405 (17.9)		
Pacific	≥55years	8,079 (7.6)		6,898 (8.2)		14,977 (7.8)		
	<55years	17,830 (24.6)		26,034 (17.7)		43,864 (20.0)		
Chinese	≥55years	9,981 (9.3)		6,881 (8.2)		16,862 (8.8)		
	<55years	2,635 (3.6)		6,882 (4.7)		9,517 (4.3)		
Indian	≥55years	4,705 (3.9)		4,035 (4.8)		8,740 (4.6)		
	<55years	2,635 (11.9)		16,159 (11)		24,806 (11.3)		
Other Asian	≥55years	4,176 (3.9)		2,653 (3.1)		6,829 (3.6)		
	<55years	4,232 (5.8)		7,664 (5.2)		11,896 (5.4)		
NZDep quintile, n (%)								<0.001
1 (least deprived)		38,831 (21.6)		50,110 (21.7)		88,941 (21.7)		
2		35,261 (19.7)		45,838 (19.8)		81,099 (19.7)		
3		32,140 (17.9)		41,112 (17.8)		73,252 (17.8)		
4		33,203 (18.5)		42,934 (18.6)		76,137 (18.5)		
5 (most deprived)		40,000 (22.3)		51,392 (22.2)		91,392 (22.3)		
Smoking, n (%)								<0.001
Never smoker		130,306 (72.6)		149,580 (64.7)		279,886 (68.1)		
Ex-smoker		27,062 (15.1)		43,448 (18.8)		70,510 (17.2)		
Current smoker		22,067 (12.3)		38,358 (16.6)		60,425 (14.7)		
Mean SBP, mmHg (SD)		129 (16.1)		129 (14.8)		129 (15.4)		<0.001
Mean DBP, mmHg (SD)		79 (9.2)		80 (9.3)		79 (9.3)		<0.001
Mean TC/HDL (SD)		3.7 (1.1)		4.4 (1.2)		4.1 (1.2)		<0.001
eGFR, ml/min (IQR)		90.1 (78.3-99.7)		91.6 (80.8-101.3)		91.0 (79.7-100.6)		<0.001
Missing value of eGFR, n (%)		33,748 (18.8)		52,038 (22.5)		85,786 (20.9)		
BMI, n (%)								<0.001
Underweight, BMI <18.5		1,840 (1.0)		790 (0.3)		2,630 (0.6)		
Normal weight, BMI 18.5-24.9		44,543 (24.8)		42,252 (18.3)		86,795 (21.1)		
Overweight, BMI 25.0-29.9		45,176 (25.2)		80,267 (34.7)		125,443 (30.5)		
Obese, BMI ≥30		57,576 (32.1)		70,996 (30.7)		128,572 (31.3)		
Mean BMI, kg/m^2		29.4		29.2		29.3		
Missing value of BMI, n (%)		30,300 (16.9)		37,081 (16.0)		67,381 (16.4)		
Diabetes (%)								<0.001
No, n (%)	Hba1c level available, n (%)	155,945 (86.9)	93,554 (60.0)	206,252 (89.1)	121,792 (59.1)	362,197 (88.2)	215,346 (59.5)	
	Hba1c mmol/mol (SD) (where available)		38.7 (6.8)		38.5 (7.5)		38.6 (7.2)	
Yes, n (%)	Hba1c level available, n (%)	23,490 (13.1)	23,067 (98.0)	25,134 (10.9)	24,697 (98.3)	48,624 (11.8)	47,764 (98.2)	

		Women		Men		Total		p-value*
	Hba1c mmol/mol (SD) (where available)		62.4 (20.5)		62.9 (20.7)		62.6 (20.6)	
Family history of premature CVD, n (%)		21,351 (11.9)		22,607 (9.7)		43,958 (10.7)		<0.001
History of atrial fibrillation, n (%)		1,140 (0.6)		2,567 (1.1)		3,707 (0.9)		<0.001
Medication at index assessment, n (%)								
Antihypertensive medication		50,934 (28.4)		50,019 (21.6)		100,953 (24.6)		<0.001
Antithrombotic medication		19,386 (10.8)		24,836 (10.7)		44,222 (10.8)		<0.001
Lipid lowering medication		32,655 (18.2)		41,432 (17.9)		74,087 (18.0)		<0.001
Absolute 5-year CVD risk %, median (IQR)		2.2 (0.8-4.0)		3.0 (1.7-5.9)		2.6 (1.5-5)		<0.001

Note: BMI=body mass index; CVD=cardiovascular disease; DBP=diastolic blood pressure; eGFR=estimated glomerular filtration rate; Hba1c=haemoglobin A1C; HDL=high-density lipoprotein; IQR=interquartile range; N=number; NZDep=The New Zealand small-area index of relative socio-economic deprivation; SBP=systolic blood pressure; SD=standard deviation, TC=total cholesterol; *p for difference between women and men

5.2.1 Demographic factors

On average women (mean age 55.7 years) were older than men (53.2 years) (p<0.001).

The participants were divided by different ethnicities and two age groups, those who were 55 years of age and over and those who were under 55 years of age. The distribution across these groups is as follows: in the 55 and over age group 67.8% (129,596) were European, 7.4% (14,233) were Māori, 7.8% (14,977) were Pacific, 8.8% (16,862) were Chinese. 4.6% (8,740) were Indian and 6,829 (3.6%) were other Asian. In the under 55 age group, the distribution was different with 41% (90,106) European, 17.9% (39,405) Māori, 20% (43,864) Pacific, 4.3% (9,517) Chinese, 11.3% (24,806) Indian and 5.4% (11,896) Other Asian.

The distribution of ethnicity for women and men is similar to each other in the 55 and over age group, with more than half of the participants European and the minority of participants were Other Asian. However, the distribution of ethnicity for women and men were different in the under 55 age group. While only 30.6% (22,204) were European in the female group, the proportion was 46.2% (67,902) in the male group (p<0.001). 23.5% and 24.6% were Māori and Pacific in the female group while the proportions were 15.2% and 17.7%, respectively, in the male group(p<0.001). The distribution of the rest of the ethnicities is similar for both sex groups (p<0.001). It is worth noting that a lot of these differences are driven by the CVD risk screening requirements in the guidelines, which are based on age, sex, ethnicity (126).

The greatest proportion of the cohort (22.3%) lived in the most deprived areas, followed by 21.7% of the cohort living in the least deprived area. 19.7%,18.5% and 17.8% of the participants were living in the second least deprived area, the second most deprived area and the third least deprived area, respectively. The distribution for women and men is similar to each other and for both sexes, the greatest proportion of the group were living in the most deprived area.

5.2.2 Societal factors and clinical characteristics

The majority of the cohort (68.1%) had never smoked, while 17.2% were ex-smokers and 14.7% were current smokers. While comparing smoking status between women and men, it is clear to see that the women smoked less than the men, with 72.6% who were never smokers in contrast to 64.7% of men having never been smokers ($p<0.001$). The proportion of ex-smoker and current smoker were around 5% higher in the male group compared to the female group ($p<0.001$).

The mean systolic blood pressure was 129 mmHg for men and women. The mean diastolic blood pressure was 79 mmHg for the total cohort. The value for the male group was 80mmHg, which was similar to that for the female group. The mean TC/HDL ratio was 4.1 for the total cohort. The ratio was 4.4 for the male group but 3.7 for the females ($p<0.001$). The median value of eGFR for the total cohort was 91 ml/min. This value was similar between men and women.

In total, a minor percentage (0.6%) of the cohort were underweight, while the largest proportion were obese (31.3%). 21.1% and 30.5% were normal weight and overweight, respectively, and the rest of the participants (16.4%) did not have the relevant data on BMI. The percentage of women who have normal weight is higher than that of men, with 24.8% compared to 18.3% ($p<0.001$). The highest proportion of men were overweight (34.7%), whereas obese women took up the highest proportion (32.1%) in the women cohort. The mean BMI value for the cohort was 29.3 kg/m^2 and the value was similar between women and men which was 29.4 kg/m^2 and 29.2 kg/m^2 respectively ($p<0.001$).

5.2.3 Comorbidities

Diabetes was present in 11.8% of the cohort. More women than men had diabetes (13.1% vs 10.9%, p<0.001). 59.5% of the participants who did not have diabetes had a record of Hba1c and the mean level was 38.6 mmol/mol (SD 7.2). For Hba1c if it is under 42 mmol/mol, it is considered at the normal range. 98.2% of the participants who had diabetes had a record of Hba1c and the mean level was 62.6 mmol/mol (SD 20.6). The percentage of women without diabetes had a record of Hba1c that was similar to that of men, at 60.0% and 59.1%, respectively (p<0.001) and the mean level of women was also similar to that of men (38.7mmol/mol vs 38.5mmol/mol). Among people with diabetes, there was no difference in the percentage of women and men who had a Hba1c test and the mean values were similar (62.4 vs 62.9 mmol/mol).

5.2.4 Medical history

Only 10.7% of the cohort had a family history of premature CVD events. Women had a higher percentage of family history of premature CVD than men with 11.9% in contrast to 9.7% (p<0.001). 0.9% of the entire cohort had a history of atrial fibrillation (AF). 1.1% of men had AF compared to 0.6% of women (p<0.001).

5.2.5 Cardiometabolic medication

24.6% of the cohort were dispensed antihypertensive medication at index assessment. Women had been dispensed more antihypertensive medication than men (28.4% vs 21.6%, p=0.02). In the case of the dispensing of antithrombotic medication, 10.8% of the entire cohort had been dispensed with antithrombotic medication and the distribution was similar in women and men. For the dispensing of lipid-lowering medication, 18.0% of the entire cohort had been dispensed to them and the distribution was similar in women and men.

5.2.6 CVD risk score

The median 5-year CVD risk score for the cohort was 2.6% (1.5-5%), indicating that half of this cohort are at more than 2.6% risk of having a CVD event within the next five years. The risk for women to have a CVD event for the following five years was 0.8% lower than that of men which was 2.2% (p<0.001).

5.3 Comparison between participants with and without a CVD event according to baseline characteristics

During 2,466,240 person-years of follow up, there were 21,937 (5.3%) patients who were having their first CVD events, 954 (0.23%) of whom had a fatal event; 9402 (2.3%) patients had a fatal non-CVD event, and the remaining 379,482 (92.4%) participants had no event by 31/12/2018. While 8,452 (2.1%) women had their first CVD event, 170,983 (41.6%) women had not experienced any event. 14,439 (3.5%) men had their first presentation of CVD while 216,947 (52.8%) had no event.

5.3.1 Female participants

In the female group, 4.7% of the participants had a CVD event including HF, CHD, Cvd, PVD, HS or CVD-related fatal death during follow up (Table 7).

Table 6 Baseline characteristics of women who had CVD event comparing to those who had non-CVD related event

		CVD event	Non-CVD related event	p-value*
Participants (percentage of total cohort)		8,452 (4.7)	170,983 (95.3)	
Mean age, years (SD)		60.3 (9.1)	55.5 (8.8)	<0.001
Prioritised self-identified ethnicity, n (%)				<0.001
European	≥55 years	3,768 (60.3)	68,376 (68.0)	
	<55years	450 (20.4)	21,754 (30.9)	
Māori	≥55years	899 (14.4)	6,857 (6.8)	
	<55years	834 (37.8)	16,212 (23.0)	
Pacific	≥55years	884 (14.2)	7,195 (7.2)	
	<55years	707 (32.1)	17,123 (24.3)	
Chinese	≥55years	253 (4.1)	9,728 (9.7)	
	<55years	19 (0.9)	2,616 (3.7)	
Indian	≥55years	315 (5.0)	4,390 (4.4)	
	<55years	146 (6.6)	8,501 (12.1)	
Other Asian	≥55years	128 (2.1)	4,048 (4.0)	
	<55years	49 (2.2)	4,183 (5.9)	
NZDep quintile, n (%)				<0.001
1 (least deprived)		1,226 (14.5)	37,605 (22.0)	
2		1,302 (15.4)	33,959 (19.9)	
3		1,380 (16.3)	30,760 (18.0)	
4		1,718 (20.2)	31,485 (18.4)	
5 (most deprived)		2,826 (33.4)	37,174 (21.7)	
Smoking, n (%)				<0.001
Never smoker		5,340 (63.2)	124,966 (73.1)	
Ex-smoker		1,410 (16.7)	25,652 (15.0)	
Current smoker		1,702 (20.1)	20,365 (11.9)	
Mean SBP, mmHg (SD)		136.0 (17.0)	128.0 (16.0)	<0.001
Mean DBP, mmHg (SD)		81.0 (10.0)	78.0 (9.0)	<0.001
Mean TC/HDL (SD)		3.9 (1.2)	3.7 (1.1)	<0.001
eGFR, ml/min (IQR)		83.4 (70.0-94.7)	90.4 (68.6-99.8)	<0.001
Missing value of eGFR, n (%)		1,375 (16.3)	32,373 (18.9)	
BMI, n (%)				<0.001

		CVD event		Non-CVD related event		p-value*
Underweight, BMI <18.5		103 (1.2)		1,737 (1.0)		
Normal weight, BMI 18.5-24.9		1,508 (17.8)		43,035 (25.2)		
Overweight, BMI 25.0-29.9		2,113 (25.0)		43,063 (25.2)		
Obese, BMI ≥30		3,683 (43.6)		53,893 (31.5)		
Missing value of BMI, n (%)		1,045 (12.4)		29,255 (17.1)		
Diabetes						<0.001
No	Hba1c level available, n (%)	6,276 (74.3)	2,923 (46.6)	149,669 (87.5)	90,631 (60.6)	
	Hba1c mmol/mol (SD) (where available)		40.5 (8.8)		38.7 (6.7)	
Yes	Hba1c level available, n (%)	2,176 (25.8)	2,132 (98.0)	21,314 (12.5)	20,935 (98.2)	
	Hba1c mmol/mol (SD) (where available)		65.5 (22.7)		62.1 (20.2)	
Family history of premature CVD, n (%)		1,244 (14.7)		20,107 (11.8)		<0.001
History of atrial fibrillation, n (%)		314 (3.7)		1,561 (0.9)		<0.001
Medication at index assessment, n (%)						
Antihypertensive medication		4,429 (52.4)		46,505 (27.2)		<0.001
Antithrombotic medication		2,201 (26.0)		17,185 (10.1)		<0.001
Lipid lowering medication		2,695 (31,9)		29,960 (17.5)		<0.001
Absolute 5-year CVD risk %, median (IQR)		5.0 (2.9-8.0)		2.1 (1.2-3.8)		<0.001

Note: BMI=body mass index; CVD=cardiovascular disease; DBP=diastolic blood pressure; eGFR=estimated glomerular filtration rate; Hba1c=haemoglobin A1C; HDL=high-density lipoprotein; IQR=interquartile range; N=number; NZDep=The New Zealand small-area index of relative socio-economic deprivation; SBP=systolic blood pressure; SD=standard deviation, TC=total cholesterol; *p for difference between women with CVD and women without CVD.

5.3.1.1 Demographic factors

The baseline mean age for women with CVD was older than women without these events (p<0.001). Compared to the group without a CVD event, the proportion of patients identifying as Māori or Pacific was higher in the CVD group regardless of the age band (P<0.001).The proportion of patients identifying as Indian and above 55 years of age was higher in the CVD group (P<0.001). The CVD event group was unevenly spread throughout the NZDep five quintiles with an skew towards the more deprived end. For those without a CVD event, the proportion in each quintile ranged from 18-22%, which was much more even than for those with a CVD event.

5.3.1.2 Societal factors and clinical characteristics

For both of the groups, the majority of women were never smokers but more participants with CVD were current smokers compared to participants without CVD (19.9 vs 11.9%, p<0.001). The value of SBP and DBP and the ratio of TC/HDL in the female group with CVD was 136 mmHg, 81.0mmHg and 3.9, respectively, which was 8mmHg, 3mmHg and 0.2 higher than that

of the group without CVD (p<0.001). In terms of BMI status, while the majority of women were obese in both groups, the percentage of the group with CVD was higher than that of the group without CVD (43.6% vs 31.5%, p<0.001). 25.8% of the women in the group with CVD had diabetes while the percentage was 12.5% in the group without diabetes. The value of mean Hba1c was 65.5 mmol/mol for women with diabetes with CVD, which was 3.4 mmol/mol higher compared to the value of the diabetic women without CVD (p<0.001). The eGFR was lower in the CVD group than in the non-CVD group (82.0ml/min vs 89 ml/min, p<0.001).

5.3.1.3 Medical history, cardiometabolic medication and CVD risk score

14.7% and 3.7% of women with CVD had a family history of premature CVD and a history of atrial fibrillation, which was all around 3% higher than that of women without CVD (p<0.001). The percentages of women with CVD using antihypertensive, antithrombotic and lipid-lowering medication were 52.4%, 26.0% and 31.9%, respectively, which were all at least two times higher than that of participants without CVD (p<0.001). Half or the women who experienced CVD were predicted to have a more than 5% risk for having a CVD risk within the next five years at baseline, which was twice the risk that had been estimated for women who did not experience CVD (p<0.001).

5.3.1.4 Follow up of non-CVD group

Within the non-CVD related group, there were 3,664 (2.1%) people who had a non-cardiac fatal event and 167,319 (97.9%) who had no event during follow up. The baseline characteristics of the group with a non-cardiac fatal event was similar to that of the group with a CVD event. Appendix 5 summarises and compares all baseline characteristics of people with a non-cardiac fatal event and no event, and significant differences can be noted.

5.3.2 Male participants

In the male group, 6.2% of them had CVD event (Table 8)

Table 7 Baseline characteristics of men who had CVD event comparing to those who had non-CVD related event

		CVD event		Non-CVD related event		p-value*
Participants (percentage of total cohort)		14,439 (6.2)		216,947 (93.8)		
Mean age, years (SD)		57.4 (9.8)		50.9 (10.0)		<0.001
Self-identified ethnicity, n (%)						<0.001
European	≥55 years	5,822 (65.3)		51,630 (68.4)		
	<55years	2,056 (37.3)		65,846 (46.5)		
Māori	≥55years	1,048 (11.8)		5,419 (7.2)		
	<55years	1,288 (23.4)		21,071 (14.9)		
Pacific	≥55years	1,080 (12.1)		5,818 (7.7)		
	<55years	1,387 (25.1)		24,647 (17.4)		
Chinese	≥55years	361 (4.1)		6,520 (8.6)		
	<55years	108 (2.0)		6,774 (4.8)		
Indian	≥55years	460 (5.2)		3,575 (4.7)		
	<55years	508 (9.2)		15,651 (11.1)		
Other Asian	≥55years	151 (1.7)		2,502 (3.3)		
	<55years	170 (3.1)		7,494 (5.3)		
NZDep quintile, n (%)						<0.001
1 (least deprived)		2,562 (17.7)		47,548 (21.9)		
2		2,475 (17.1)		43,363 (20.0)		
3		2,432 (16.8)		38,680 (17.8)		
4		2,893 (20.0)		40,041 (18.5)		
5 (most deprived)		4,077 (28.0)		47,315 (21.8)		
Smoking, n (%)						<0.001
Never smoker		8,062 (55.8)		141,518 (65.2)		
Ex-smoker		3,214 (22.3)		40,234 (18.6)		
Current smoker		3,163 (21.9)		35,195 (16.2)		
Mean SBP, mmHg (SD)		135.0 (16.4)		128.0(14.6)		<0.001
Mean DBP, mmHg (SD)		82.0 (10.1)		80.0 (9.2)		<0.001
Mean TC/HDL (SD)		4.5 (1.3)		4.4 (1.2)		=0.28
eGFR, ml/min (IQR)		86.7 (74.4-96.6)		91.8 (81.1-101.5)		<0.001
Missing value of eGFR, n (%)		2,681 (18.6)		49,357 (22.8)		
BMI, n (%)						<0.001
Underweight, BMI <18.5		61 (0.4)		729 (0.3)		
Normal weight, BMI 18.5-24.9		2,196 (15.2)		40,056 (18.5)		
Overweight, BMI 25.0-29.9		4,847 (33.6)		75,420 (34.8)		
Obese, BMI ≥30		5,801 (40.2)		65,195 (30.1)		
Missing value of BMI, n (%)		1,534 (10.6)		35,547 (16.4)		
Diabetes						<0.001
No, n (%)	Hba1c level available, n (%)	11,185 (77.5)	5,225 (46.7)	195,067 (89.9)	116,567 (59.8)	
	Hba1c mmol/mol (SD) (where available)		40.2 (9.4)		38.5 (7.4)	
Yes, n (%)	Hba1c level available, n (%)	3,254 (22.5)	3.204 (98.5)	21,880 (10.1)	21,493 (98.2)	
	Hba1c mmol/mol (SD) (where available)		65.9 (22.2)		62.4 (20.4)	
Family history of premature CVD, n (%)		1,830 (12.7)		20,777 (9.6)		<0.001
History of atrial fibrillation, n (%)		630 (4.4)		3,241 (1.5)		<0.001
Medication at index assessment, n (%)						
Antihypertensive medication		6,095 (42.2)		43,924 (20.3)		<0.001
Antithrombotic medication		3,495 (24.2)		21,341 (9.8)		<0.001
Lipid lowering medication		4,405 (30.5)		37,027 (17.1)		<0.001
Absolute 5-year CVD risk %, median (IQR)		6.8 (3.9-10.8)		2.9 (1.6-5.4)		<0.001

Note: BMI=body mass index; CVD=cardiovascular disease; DBP=diastolic blood pressure; eGFR=estimated glomerular filtration rate; Hba1c=haemoglobin A1C; HDL=high-density lipoprotein; IQR=interquartile range; N=number; NZDep=The New Zealand small-area index of relative socio-economic deprivation; SBP=systolic blood pressure; SD=standard deviation, TC=total cholesterol; *p for difference between men who had CVD event and those who had non-CVD related event.

5.3.2.1 Demographic factors

In the male group, 6.2% had a CVD event and their mean age was 57.4, which was 6.5 years older than men without a CVD event ($p<0.001$). While in both the 55 and the over age group and the under 55 age group, European patients comprised the major part, the percentage of Māori and Pacific patients was higher in the group with CVD than the group without CVD ($p<0.001$). In terms of the NZDep quintile, the uneven distribution is highlighted by the highest proportion at 28% in the most deprived quintile in the male group with CVD, while the percentage was relatively evenly distributed in the male group without CVD despite this statistically significant difference ($p<0.001$).

5.3.2.2 Societal factors and clinical characteristics

The percentage of ex-smokers and current smokers was 22.3% and 21.9%, respectively, in men with CVD and it was higher than that in the group without CVD ($p<0.001$). The value of SBP was overall higher in the CVD group and compared to the non-CVD group, the difference was 9 mmHg ($p<0.001$). The value of DBP was similar between men who had a CVD event and men who had a non-CVD related event. The comparison of value of TC/HDL between men who had a CVD event and men who had a non-CVD related event was not statistically significant ($p=0.28$).

Obese men comprised the largest part in the CVD group and it was 10% higher than obese men in the non-CVD group ($p<0.001$). The percentage of men who had diabetes in the CVD group was two times higher than that in the non-CVD group and the mean value of Hba1c was around 4mmol/mol higher in the CVD group for those with and without diabetes ($p<0.001$). The eGFR was 86.7 in the CVD group, which was 5.7 lower in the non-CVD group ($p<0.001$).

5.3.2.3 Medical history, cardiometabolic medication and CVD risk score

In terms of the family history of premature CVD and the history of atrial fibrillation, the percentage was 12.7 and 4.4 in the CVD group, while it was 9.6 and 1.5, respectively, in the non-CVD group ($p<0.001$). Regarding the use of antihypertensive, antithrombotic and lipid-lowering medication, the percentage was 42.2%, 24.2% and 30.5% respectively, which was

more than two times higher in the CVD group compared to the non-CVD group (p<0.001). Lastly, half of the participants with CVD was estimated with more than 6.8% of risk of having CVD within the next five years and the estimated median risk for participants without CVD was halved (2.9%) (p<0.001).

5.3.2.4 Comparison within non-CVD related group

There were 4,784 (2.2%) men having a non-cardiac fatal event and 212,163 (97.8) having no event at all. The distribution of risk factors in the non-cardiac fatal group was similar to that in the CVD group. Appendix 6 summarises and compares all baseline characteristics of people with non-cardiac fatal event and no event. Although the significant differences can be noticed, the value was not always higher in the non-cardiac fatal event group compared to that in the no event group. For example, the two groups had the same mean DBP. The group without any event had a higher TC/HDL ratio and a higher percentage of obese people.

5.4 Comparison between participants with heart failure and participants with other CVD event according to baseline characteristics

This part will compare the baseline characteristics of participants with HF and that of the participants with other events including CHD, Cevd, PVD, HS, and fatal event including cardiac-related fatal event and non-cardiac related fatal event. The comparison will be first made between HF and the other four CVD events (CHD, Cevd, PVD and HS) and then the comparison will be made between HF and each of other events. The comparison will be depicted by sex.

5.4.1 The outcome of female group

In total, there were 12,116 females having indicated a type of CVD events and fatal events (Table 11). 1,505 (12.4%) females had HF compared to 6,693 (55.2%) females who had the rest of the non-fatal CVD events. While the majority had coronary heart disease and non-cardiac death, which comprised 27.9% and 30.2% of this female cohort, respectively. CVD death and haemorrhagic stroke were the least common outcome among these women, as there were only 2.1% and 4.1% of females who had them. The rest of the females had cerebrovascular disease (18.3%) and peripheral vascular disease (5.0%).

5.4.1.1 HF group in comparison to the combined group of the other four CVD events according to baseline characteristics

In the female group, 1,505 (12.4%) participants had HF comparing to 6,693 (55.2%) had the rest of the non-fatal CVD event (Table 9).

Table 8 Baseline characteristics of women with HF comparing to women with other four CVD combined

		Heart Failure		**Four CVD combined**		**P-value***
Participants (percentage of total cohort)		1,505 (13.4)		6,693 (81.6)		
Mean age, years (SD)		60.6 (9.2)		60.2 (9.1)		=0.1
Prioritised self-identified ethnicity, n(%)						<0.001
European	≥55 years	551 (50.1)		3,092 (62.6)		
	<55years	47 (11.6)		392 (22.4)		
Māori	≥55years	234 (21.3)		627 (12.7)		
	<55years	163 (40.4)		651 (37.1)		
Pacific	≥55years	227 (20.6)		626 (12.7)		
	<55years	173 (42.8)		519 (29.6)		
Chinese	≥55years	21 (1.9)		229 (4.6)		
	<55years	2 (0.5)		17 (1.0)		
Indian	≥55years	49 (4.5)		260 (5.3)		
	<55years	13 (3.2)		132 (7.5)		
Other Asian	≥55years	19 (1.7)		106 (2.1)		
	<55years	6 (1.5)		42 (2.4)		
NZDep quintile, n (%)						<0.001
1 (least deprived)		171 (11.3)		1,026 (15.3)		
2		188 (12.5)		1,089 (16.3)		
3		225 (15.0)		1,109 (16.6)		
4		287 (19.1)		1,379 (20.6)		
5 (most deprived)		634 (42.1)		2,090 (31.2)		
Smoking, n (%)						=0.62
Never smoker		953 (63.3)		4,240 (63.4)		
Ex-smoker		264 (17.5)		1,117 (17.0)		
Current smoker		288 (19.1)		1,336 (20.0)		
Mean SBP, mmHg (SD)		137.0 (17.4)		136.0 (17.4)		=0.03
Mean DBP, mmHg (SD)		81.0 (10.1)		80.0 (10.0)		=0.04
Mean TC/HDL (SD)		3.7 (1.2)		4.0 (1.2)		<0.001
eGFR, ml/min (IQR)		82.7 (69.0-95.0)		83.6 (70.3-94.7)		<0.001
Missing value of eGFR, n (%)		214 (14.2)		1,121 (16.7)		
BMI						<0.001
Underweight, BMI <18.5		25 (1.7)		75 (1.1)		
Normal weight, BMI 18.5-24.9		160 (10.6)		1,296 (19.4)		
Overweight, BMI 25.0-29.9		248 (16.5)		1,824 (27.3)		
Obese, BMI ≥30		916 (60.7)		2,667 (40.0)		
Missing value of BMI, n (%)		156 (10.4)		831 (12.4)		
Diabetes (%)						
No, n (%)	Hba1c level available, n (%)	1,053 (70.0)	493 (46.8)	5,024 (75.1)	2,331 (46.4)	<0.001
	Hba1c mmol/mol (SD) (where available)		41.4 (9.5)		40.3 (8.8)	=0.01
Yes, n (%)	Hba1c level available, n (%)	452 (30.0)	443 (98.0)	1,669 (25.0)	1,637 (98.1)	<0.001
	Hba1c mmol/mol (SD) (where available)		66.2 (24.2)		65.5 (22.4)	=0.61

	Heart Failure	Four CVD combined	P-value*
Family history of premature CVD, n (%)	183 (12.2)	1,034 (15.5)	=0.001
History of atrial fibrillation, n (%)	105 (7.0)	267 (4.0)	<0.001
History of cardiomyopathy, n (%)	5 (0.3)	17 (0.3)	=0.6
History of cardiac valve prosthesis or device (ICD or pacemaker) implanted, n (%)	15 (1.0)	20 (0.3)	<0.001
History of valve disease,n (%)	23 (1.5)	25 (0.4)	<0.001
Medication at index assessment, n (%)			
Antihypertensive medication	870 (57.8)	3,414 (51.0)	<0.001
Antithrombotic medication	483 (32.1)	1,658 (24.8)	<0.001
Lipid lowering medication	524 (34.8)	2,099 (31.4)	<0.001
Absolute 5-year CVD risk %, median (IQR)	5.7 (3.4-8.9)	4.8 (2.7-7.6)	<0.001

Note: BMI=body mass index; CVD=cardiovascular disease; DBP=diastolic blood pressure; eGFR=estimated glomerular filtration rate; Hba1c=haemoglobin A1C; HDL=high-density lipoprotein; IQR=interquartile range; N=number; NZDep=The New Zealand small-area index of relative socio-economic deprivation; SBP=systolic blood pressure; SD=standard deviation, TC=total cholesterol; *p for difference between women with HF and women with other four non-fatal CVD.

5.4.1.2 HF group in comparison to each of the event group according to baseline characteristics

5.4.1.2.1 Demographic factors

The mean age for women who had HF was 60.6 years of age (SD 9.2) and the mean age for women who had the remaining four CVD events was 60.2 years of age (SD 9.1) (P=0.10).

In the 55 and over age band, 1,101 (18.2%) females had HF. In terms of ethnicity, European patients comprised the largest proportion of the HF group (50.1%). Both Māori and Pacific patients comprised around one fifth of the groups, respectively. Indian, Chinese and other Asian comprised the rest of the proportion at 4.5%, 1.9% and 1.7%. While comparing to the four CVD events combined group where 62.6% were European people, the proportion of Māori and Pacific patients who had HF was almost 10% higher (p<0.001).

In the under 55 age band, the highest proportion of women having HF were Māori and Pacific, who comprised 40.4% and 42.8%. Only 11.6% of European women had HF. Indian, other Asian and Chinese comprised 3.2%, 1.5% and 0.5% of the proportion. The proportion of European females having the other four CVD events was 10% higher than that of European females who had HF(22.4% vs 11.6%, p<0.001), while the proportion of Pacific females having the other four CVD events was around 13% lower than that of Pacific females who had HF (29.6% vs 42.8%, p<0.001).

42.1% of women with HF were living in the most deprived areas, which was 4 times higher than their counterparts who were living in the least deprived areas (42.1% vs 11.3%, p<0.001). The proportion of women with HF increased from 12.5% to 19.1% gradually along the second, third and fourth quintile. While the proportion of women who had the other four CVD events living in the least deprived area was slightly higher than that of women who had HF (15.3% vs 11.3%, p<0.001), the proportion of women who had the other four CVD events living in the most deprived areas was more than 10% lower than that of women who had HF (31.2% vs 42.1%, p<0.001).

5.4.1.2.2 Societal factors and clinical characteristics

The percentage for HF women classified as current smoker was 19.1%, while the percentage for the current smokers in the four combined CVD events group was 20.0%, but the differences were not statistically significant (P=0.62).

The mean SBP for HF women was 137.0mmHg (SD17.4), which was similar to the mean SBP for the four CVD events combined group (136.0mmHg,SD17.1) (p=0.03). The mean DBP 81.0mmHg (SD 10.1) for the HF group was similar to the other CVD combined group (p=0.04). The mean TC/HDL ratio for the HF group was 3.7 (SD1.2) which was similar to that for the female group who had the other four CVD events (p<0.001). The EGFR for the HF group was 82.7 ml/min as the medium value, which was similar to that of the four CVD events combined group (p<0.001).

60.7% of HF women were obese, 10.6% of them were normal and 16.5% were overweight. The proportion of obese women having the other four CVD events was 39.9% which was more than 20% lower than that of the HF women (p<0.001).

5.4.1.2.3 Comorbidities

In the HF group, the proportion of women having a history of diabetes was 30.0%, which was 5% higher than that of the four CVD events combined group (30% vs 25%, p<0.001). 46.8% of women in the HF group had Hba1c test without diabetes and the proportion in the four CVD events combined group was 46.4%. The average level of Hba1c was 41.4 mmol/mol in the HF group which was similar to that in the four CVD events combined group (40.3mmol/mol) (p=0.01). 98.0% of HF women with diabetes and the same proportion of diabetic women with

the other four CVD events had Hba1c test. The comparison between the average level of Hba1c in the HF group and that in the four CVD events combined group was not statistically significant(p=0.61).

5.4.1.2.4 Medical history

12.2% of HF women had a family history of premature CVD, which was 3.4% lower than the proportion of women who had the other four CVD events with a family history of premature CVD (p=0.001). 7.0% of HF women had a history of atrial fibrillation, which was 3% higher than the proportion of women who had the other four CVD events (p<0.001). 0.3% of HF women had a history of cardiomyopathy and the percentage was the same for the four CVD events combined group, but the comparison was not statistically significant (p=0.6). The percentage of having a history of prosthesis or cardiac device implanted was 1 for the HF group comparing to the 0.3% for the combined group (p<0.001). 1.5% of HF women had a history of valve disease and this was 1.1% higher than that of the combined group (p<0.001).

5.4.1.2.5 Cardiometabolic medication

While 57.8% of HF patients had been dispensed antihypertensive medication, 32.1% had been dispensed antithrombotic medication and 34.8% had been dispensed lipid-lowering medication, 51% of women with other four CVD had been dispensed antihypertensive medication, 24.8% had been dispensed antithrombotic medication and the percentage of women dispensed lipid-lowering medication was similar to that of women with HF (31.4%) (p<0.001).

5.4.1.2.6 CVD risk score

For half of women who developed HF, there was at least a 5.7% risk of having CVD within the next five years while the risk was at least 4.8% for half of women who developed the other four CVD events (p<0.001).

5.4.1.3 HF group in comparison to each of the event group according to baseline characteristics

In the female group, 12.4% had HF and CHD and non-cardiac fatal event comprised the largest proportion (27.9% and 30.2%) (Table 10).

Table 9 Baseline characteristics of women with HF comparing to women with each of the other event

Participants		**Female**							**p-value***
		Non-fatal CVD event					**Fatal event**		
		Heart failure	**Coronary heart disease**	**Cerebrovascular disease**	**Peripheral vascular disease**	**Haemorrhagic stroke**	**Cardiac**	**Non-cardiac**	
Participants (percentage of total cohort)		1,505 (12.4)	3,382 (27.9)	2,215 (18.3)	602 (5.0)	494 (4.1)	254 (2.1)	3,664 (30.2)	
Mean age, years (SD)		60.6 (9.2)	59.9 (9.0)	60.6 (9.3)	60.9 (9.3)	59.5 (9.0)	62.0 (8.9)	61.2 (8.5)	<0.001
Prioritised self-identified ethnicity, n (%)									<0.001
European	≥55 years	551 (50.1)	1,548 (62.3)	1,042 (63.0)	305 (67.5)	197 (56.3)	125 (60.7)	1,851 (63.6)	
	<55years	47 (11.6)	207 (23.1)	107 (19.0)	48 (32.0)	30 (20.8)	11 (22.9)	193 (25.6)	
Māori	≥55years	234 (21.3)	319 (12.8)	211 (12.8)	62 (13.7)	35 (10.0)	38 (18.5)	464 (16.0)	
	<55years	163 (40.4)	324 (36.1)	212 (37.7)	61 (40.7)	54 (37.5)	20 (41.7)	284 (37.6)	
Pacific	≥55years	227 (20.6)	312 (12.6)	215 (13.0)	51 (11.3)	48 (13.7)	31 (15.1)	380 (13.1)	
	<55years	173 (42.8)	262 (29.2)	188 (33.5)	31 (20.7)	38 (26.4)	15 (31.3)	217 (28.7)	
Chinese	≥55years	21 (1.9)	102 (4.1)	83 (5.0)	10 (2.2)	34 (9.7)	3 (1.5)	99 (3.4)	
	<55years	2 (0.5)	8 (0.9)	6 (1.1)	1 (0.7)	2 (1.4)	0 (0)	17 (2.3)	
Indian	≥55years	49 (4.5)	155 (6.2)	70 (4.2)	19 (4.2)	16 (4.6)	6 (2.9)	66 (2.3)	
	<55years	13 (3.2)	77 (8.6)	38 (6.8)	5 (3.3)	12 (8.3)	1 (2.1)	26 (3.4)	
Other Asian	≥55years	19 (1.7)	49 (2.0)	32 (1.9)	5 (1.1)	20 (5.7)	3 (1.5)	49 (1.7)	
	<55years	6 (1.5)	19 (2.1)	11 (2.0)	4 (2.7)	8 (5.6)	1 (2.1)	18 (2.4)	
NZDep quintile, n (%)									<0.001
1 (least deprived)		171 (11.3)	499 (14.8)	355 (16.0)	92 (15.3)	80 (16.2)	29 (11.4)	568 (15.5)	
2		188 (12.5)	544 (16.1)	372 (16.8)	96 (16.0)	77 (15.6)	25 (9.8)	575 (15.7)	
3		225 (15.0)	564 (16.7)	374 (16.9)	85 (14.1)	86 (17.4)	46 (18.1)	613 (16.7)	
4		287 (19.1)	738 (21.8)	417 (18.8)	132 (21.9)	92 (18.6)	52 (20.5)	795 (21.7)	
5 (most deprived)		634 (42.1)	1,037 (30.7)	697 (31.5)	197 (32.7)	159 (32.2)	102 (40.2)	1,113 (30.4)	
Smoking, n (%)									<0.001
Never smoker		953 (63.3)	2,151 (63.6)	1,490 (67.3)	285 (47.3)	314 (63.6)	147 (57.9)	2,184 (59.6)	
Ex-smoker		264 (17.5)	602 (17.8)	341 (15.4)	104 (17.3)	70 (14.2)	29 (11.4)	712 (19.4)	
Current smoker		288 (19.1)	629 (18.6)	384 (17.3)	213 (35.4)	110 (22.3)	78 (30.7)	768 (21.0)	
Mean SBP, mmHg (SD)		137.0 (17.4)	136.0 (16.2)	136.0 (17.4)	138.0 (19.2)	137.0 (18.8)	139 (16.8)	133.0 (16.7)	<0.001
Mean DBP, mmHg (SD)		81.0 (10.1)	80.0 (9.3)	81.0 (9.8)	81.0 (10.9)	83.0 (11.7)	83.0 (10.2)	79.0 (9.3)	<0.001
Mean TC/HDL (SD)		3.7 (1.2)	4.0 (1.2)	3.9 (1.2)	4.1 (1.4)	3.8 (1.2)	4.1 (1.2)	3.8 (1.3)	<0.001
eGFR, ml/min (IQR)		82.7 (69.0-95.0)	83.6 (70.4-94.8)	83.4 (70.0-94.2)	81.8 (67.4-94.0)	87.5 (72.3-96.2)	83.7 (69.0-94.4)	84.2 (71.2-95.3)	<0.001
Missing value of eGFR, n (%)		214 (14.2)	586 (17.3%)	366 (16.5)	84 (14.0)	85 (17.2)	40 (15.7)	585 (16.0)	

		Non-fatal CVD event										Fatal event				p-value*
		Heart failure		Coronary heart disease		Cerebrovascular disease		Peripheral vascular disease		Haemorrhagic stroke		Cardiac		Non-cardiac		
BMI, n (%)																<0.001
Underweight, BMI <18.5		25 (1.7)		33 (1.0)		21 (1.0)		11 (1.8)		10 (2.0)		3 (1.2)		86 (2.4)		
Normal weight, BMI 18.5-24.9		160 (10.6)		626 (18.5)		422 (19.1)		131 (21.8)		117 (23.7)		52 (20.5)		783 (21.4)		
Overweight, BMI 25.0-29.9		248 (16.5)		914 (27.0)		628 (28.4)		166 (27.6)		116 (23.5)		41 (16.1)		817 (22.3)		
Obese, BMI ≥30		916 (60.7)		1,402 (41.5)		867 (39.1)		223 (37.0)		175 (35.4)		100 (39.4)		1,268 (34.6)		
Missing value of BMI, n (%)		156 (10.4)		407 (12.0)		277 (12.5)		71 (11.8)		76 (15.4)		58 (22.8)		710 (19.4)		
Diabetes																
No, n (%)	Hba1c level available, n (%)	1,053 (70.0)	493 (46.8)	2,519 (74.5)	1,167(46.3)	1,714 (77.4)	786 (46.9)	384 (63.8)	185 (48.1)	407 (82.4)	193 (47.4)	199 (78.4)	99 (49.7)	2,921 (79.7)	1,456 (49.8)	<0.001
	Hba1c mmol/mol (SD) (where available)		41.4 (9.5)		40.3 (8.7)		40.6 (10.2)		40.0 (6.0)		39.6 (4.5)		40.2 (4.7)		39.9 (9.3)	=0.04
Yes, n (%)	Hba1c level available, n (%)	452 (30.0)	443 (98.0)	863 (25.5)	850 (98.4)	501 (22.6)	487 (97.2)	218 (36.2)	215 (98.6)	87 (17.6)	85 (97.7)	55 (21.7)	52 (94.5)	743 (20.3)	727 (97.8)	<0.001
	Hba1c mmol/mol (SD) (where available)		66.2 (24.2)		65.4 (22.2)		65.2 (22.3)		69.6 (24.4)		58.6 (19)		59.2 (19.2)		61.5 (20.5)	<0.001
Family history of premature CVD, n (%)		183 (12.2)		577 (17.1)		287 (13.0)		94 (15.6)		76 (15.4)		27 (10.6)		431 (11.8)		<0.001
History of atrial fibrillation, n (%)		105 (7.0)		77 (2.3)		90 (4.1)		23 (3.8)		10 (2.0)		9 (3.5)		85 (2.3)		<0.001
History of cardiomyopathy, n (%)		5 (0.3)		8 (0.2)		6 (0.3)		1 (0.2)		2 (0.4)		0		2 (0.1)		=0.26
History of cardiac valve prosthesis or device (ICD or pacemaker) implanted, n (%)		15 (1.0)		10 (0.3)		6 (0.3)		3 (0.5)		1 (0.2)		0		9 (0.3)		<0.001
History of valve disease,n (%)		23 (1.5)		13 (0.4)		10 (0.5)		1 (0.2)		1 (0.2)		0		9 (0.3)		<0.001
Medication at index assessment, n (%)																
Antihypertensive medication		870 (57.8)		1,737 (51.4)		1,089 (49.2)		370 (61.4)		218 (44.1)		145 (57.1)		1,565 (42.7)		<0.001
Antithrombotic medication		483 (32.1)		838 (24.8)		522 (23.6)		190 (31.6)		108 (21.9)		60 (23.6)		719 (19.6)		<0.001
Lipid lowering medication		524 (34.8)		1,097 (32.4)		664 (29.8)		212 (35.2)		126 (25.5)		72 (28.4)		985 (26.9)		<0.001
Absolute 5-year CVD risk %, median (IQR)		5.7 (3.4-8.9)		4.7 (2.7-7.5)		4.8 (2.6-7.5)		6.2 (3.9-9.8)		4.3 (2.3-7.0)		6.3 (3.8-10.1)		4.6 (2.6-7.4)		<0.001

Note: BMI=body mass index; CVD=cardiovascular disease; DBP=diastolic blood pressure; eGFR=estimated glomerular filtration rate; Hba1c=haemoglobin A1C; HDL=high-density lipoprotein; IQR=interquartile range; N=number; NZDep=The New Zealand small-area index of relative socio-economic deprivation; SBP=systolic blood pressure; SD=standard deviation, TC=total cholesterol; *p for difference between women with HF and women with each of the other events.

5.4.1.3.1 Demographic factors

The mean age for women who had HF was same as the mean age for those who had Cevd (SD 9.3), but younger than those who had PVD with a mean age of 60.9 years (SD 9.3) and who had fatal events with a mean age of 62.0 years (SD 8.9) for cardiac death and a mean age of 61.2 for non-cardiac death (SD8.5). In contrast, women who had CHD and HS were slightly younger than those who had HF, as for both their mean age was 59.9 (SD 9.0) ($p<0.001$).

While comparing the 55 and over age group across outcome event groups, the proportion of European women in the other event groups was almost 10% higher than that of the HF group. However, the proportion of both Māori and Pacific with HF was nearly two times higher than that of other CVD events ($p<0.001$). In the under 55 age group, the proportion of European women in the other event groups was nearly two times higher than that of the HF group. While the proportion of Māori women was similar across the different outcome groups, the proportion of Pacific women was nearly 10% higher than that of the other groups ($p<0.001$).

While looking at the distribution of NZDep, it was similar for women who had cardiac death in comparison to their HF counterparts. The proportion of women having HF was nearly 10% higher than the other women having other CVD events and non-cardiac death living in the most deprived areas ($p<0.001$).

5.4.1.3.2 Societal factors and clinical characteristics

The percentage for HF women classified as current smoker was only slightly higher than that of CHD and Cevd women (18.6% & 17.3%), but it was more than 10% lower than that of PVD and cardiac-death ($p<0.001$).

The mean SBP for HF women was similar to other events. Similarly, the mean DBP for the HF group was comparable to the mean value of the other event. The mean TC/HDL ratio was similar across all event groups. The medium value of eGFR for the HF group was similar to that of all groups except for the group with PVD which was 87.5 ml/min ($P<0.001$).

The distributions by BMI status for HF females was significantly different from that in other six events groups, the percentage that females with HF who were obese was more than 20%

higher than that of the other groups, which also explains the lower percentage of normal weight and overweight in HF group compared to the other groups ($p<0.001$).

5.4.1.3.3 Comorbidities

The proportion of HF women having diabetes was higher than most of the outcome groups but was lower than the PVD group which was 36.2%. The proportion of women having Hba1c test without diabetes was similar across these groups, and the value of Hba1c level was similar across these seven groups. The proportion of diabetic women having Hba1c test was similar across the groups. The average level of Hba1c for HF women having diabetes was only 3.5mmol/mol lower than that for PVD men having diabetes but similar to that for men with CHD and Cevd having diabetes and 4.7-7.6mmol/mol higher than that of the other CVD groups ($p<0.001$).

5.4.1.3.4 Medical history

The proportion of HF women having a family history of premature was similar across all event groups. 7.0% of HF women had a history of atrial fibrillation, which was more than three times higher than that of CHD,HS and the non-cardiac death group was more than 3% higher than the Cevd, PVD and cardiac-death group ($p<0.001$). The differences in the percentage of patients having a history of cardiomyopathy between the women with HF and the women with other event were not statistically significant ($p=0.26$). 1% of HF women had a history of prosthesis or cardiac device implanted, which was at least two times higher than the rest of all event groups ($P<0.001$). Out of all event groups, the HF group had the highest proportion of patients having a history of valve disease as well and it was 4-7 times higher than that of the other groups ($p<0.001$).

5.4.1.3.5 Cardiometabolic medication

57.8% of HF patients had been dispensed antihypertensive medication, which was similar to that of women with fatal cardiac event who were dispensed the same medication but it was approximately 10% higher than other groups except for the PVD patients with 61.4% having been dispensed antihypertensive medication ($p<0.001$). 32.1% of HF patients had been dispensed antithrombotic medication, which was similar to that of women with PVD having been dispensed the same medication and it was almost 10% higher than the figures in the rest of the other groups ($p<0.001$). 34.8% of HF patients had been dispensed lipid lowering

medication, which was similar to that of women with CHD, Cevd, PVD dispensed the same medication but it was 6.4-9.3% higher than that of women with other CVD event (p<0.001).

5.4.1.3.6 CVD risk score

The 5 year CVD risk score for women demonstrate that half those who developed HF would have a at least 5.7% risk for having a CVD event, which was slightly higher than the other groups except for the group with PVD and those who died due to cardiac events (6.2% and 6.3%, respectively) (p<0.001).

5.4.2 The outcome of male group

In total, there were 19,223 male having five types of CVD events and fatal events (Table 12). 2,000 (10.4%) of them had HF compared to 11,739 (61.1%) having the rest of the four non-fatal CVD events. People who had coronary heart disease and non-cardiac death comprised the largest proportion of the male group, at 37.3% and 24.9%, respectively. 15.2% had cerebrovascular disease and 5.6% had peripheral vascular disease. Only 2.9% of the males had haemorrhagic stroke and the rest 3.6% were dead due to cardiac events.

5.4.2.1 HF group in comparison to the combined group of the other four CVD events according to baseline characteristics (Table 11)

In the male group, 2000 (10.4%) had HF while 11,739 (61.1%) had the other four non-fatal CVD events (Table 11).

Table 10 Baseline characteristics of men with HF comparing to men with other four CVD combined

		HF	**Four CVD combined**	**p-value***
Participants (percentage of total cohort)		2,000 (14.6)	11,739 (85.4)	
Mean age, years (SD)		57.1 (10.7)	57.5 (9.7)	0.06
Prioritised self-identified ethnicity, n(%)				<0.001
European	≥55 years	660 (55.1)	4,879 (66.9)	
	<55years	180 (22.4)	1,783 (40.1)	
Māori	≥55years	246 (20.5)	733 (10.1)	
	<55years	319 (40.0)	872 (19.6)	
Pacific	≥55years	222 (18.5)	801 (11.0)	
	<55years	271 (33.8)	1,049 (23.6)	
Chinese	≥55years	28 (2.3)	329 (4.5)	
	<55years	7 (0.9)	99 (2.2)	
Indian	≥55years	34 (2.8)	418 (5.7)	
	<55years	21 (2.6)	476 (10.7)	
Other Asian	≥55years	8 (0.7)	137 (1.9)	
	<55years	4 (0.5)	163 (3.7)	

		HF		Four CVD combined		p-value*
NZDep quintile, n (%)						<0.001
1 (least deprived)		224 (11.2)		2,238 (19.1)		
2		274 (13.7)		2,099 (17.9)		
3		299 (15.0)		2,038 (17.4)		
4		394 (19.7)		2,342 (20.0)		
5 (most deprived)		809 (40.5)		3,022 (25.7)		
Smoking, n (%)						<0.001
Never smoker		1,004 (50.2)		6,713 (57.2)		
Ex-smoker		502 (25.1)		2,566 (21.9)		
Current smoker		494 (24.7)		2,460 (21.0)		
Mean SBP, mmHg (SD)		137.0 (16.8)		135 (16.2)		<0.001
Mean DBP, mmHg (SD)		83.0 (10.9)		82.0 (9.9)		<0.001
Mean TC/HDL (SD)		4.2 (1.3)		4.5 (1.3)		<0.001
eGFR, ml/min (IQR)		87.9 (74.0-98.1)		86.2 (74.4-96.3)		<0.001
Missing value of eGFR, n (%)		312 (15.6)		2,217 (18.9)		
BMI						<0.001
Underweight, BMI <18.5		10 (0.5)		44 (0.4)		
Normal weight, BMI 18.5-24.9		200 (10.0)		1,910 (16.3)		
Overweight, BMI 25.0-29.9		439 (22.0)		4,204 (35.8)		
Obese, BMI ≥30		1,172 (58.6)		4,342 (37.0)		
Missing value of BMI, n (%)		179 (9.0)		1,239 (10.6)		
Diabetes (%)						
No, n (%)	Hba1c level available, n (%)	1,469 (73.5)	725 (49.4)	9,137 (77.8)	4,226 (46.3)	<0.001
	Hba1c mmol/mol (SD) (where available)		41.2 (10.6)		40.1 (9.0)	=0.003
Yes, n (%)	Hba1c level available, n (%)	531 (26.6)	523 (98.5)	2,602 (22.1)	2,563 (98.5)	<0.001
	Hba1c mmol/mol (SD) (where available)		68.0 (23.9)		65.5 (21.9)	=0.02
Family history of premature CVD, n (%)		203 (10.2)		1,559 (13.3)		<0.001
History of atrial fibrillation, n (%)		179 (9.0)		431 (3.7)		<0.001
History of cardiomyopathy, n (%)		19 (1.0)		17 (0.1)		<0.001
History of cardiac valve prosthesis or device (ICD or pacemaker) implanted, n (%)		25 (1.3)		43 (0.4)		<0.001
History of valve disease,n (%)		27 (1.4)		35 (0.3)		<0.001
Medication at index assessment, n (%)						
Antihypertensive medication		1,007 (50.4)		4,802 (40.9)		<0.001
Antithrombotic medication		562 (28.1)		2,778 (23.7)		<0.001
Lipid lowering medication		601 (30.1)		3,614 (30.8)		<0.001
Absolute 5-year CVD risk %, median (IQR)		7.9 (4.5-12.1)		6.6 (3.8-10.5)		<0.001

Note: BMI=body mass index; CVD=cardiovascular disease; DBP=diastolic blood pressure; eGFR=estimated glomerular filtration rate; Hba1c=haemoglobin A1C; HDL=high-density lipoprotein; IQR=interquartile range; N=number; NZDep=The New Zealand small-area index of relative socio-economic deprivation; SBP=systolic blood pressure; SD=standard deviation, TC=total cholesterol; *p for difference between men with HF and men with the other four non-fatal CVD.

5.4.2.1.1 Demographic factors

The mean age for men who had HF was 57.1 (SD 10.7) years, but it was 57.5 (SD 9.7) years for men who had the other four CVD events (p=0.06).

In the 55 and over age band, 1,198 males had HF with European patients comprising the largest proportion (55.1%). Both Māori and Pacific patients comprised around one fifth of the groups, respectively. Indian, Chinese and other Asian comprised the rest of the proportion at 2.8%, 2.3% and 0.7%. The proportion of Māori patients having HF was 10.4% higher than that of Māori patients having the other four CVD events and the difference between the proportion of Pacific patients having HF and that of Pacific patients having four CVD events was 7.5% (p<0.001). In the under 55 age band, the Māori group comprised the largest proportion of men having HF (40.0%), while the Pacific group comprised around one third (33.8%) and the European group comprised around one fifth (22.4%). The rest 2.6%, 0.9% and 0.5% were comprised by Indian, Chinese and other Asian, respectively. The proportion of Māori, Pacific and Indian males having the other four CVD events was 20.2%, 10.2% and 8.1% lower than that of Māori and Pacific males who had HF, respectively (p<0.001).

40.5% of men with HF were living in the most deprived areas, which was almost four times higher than their counterparts who were living in the least deprived areas (11.2%). The proportion of men with HF increased from 13.7% to 19.7% gradually along the second, third and fourth quintile. The proportion of men who had the other four CVD events living in the most deprived areas was more than 15% lower than that of men who had HF (p<0.001).

5.4.2.1.2 Societal factors and clinical characteristics

The percentage for HF men who were never smokers, ex-smokers and current smokers was 50.2%, 25.1% and 24.7%, which was similar to the percentage of male current smokers who had the other four CVD events (p<0.001).

The mean SBP of HF men was 137.0 mmHg (SD 16.8), which was similar to the mean SBP of men who had the other four CVD events. The means of DBP between men who had HF and the men who had the other four CVD events was similar as well. The mean TC/HDL ratio for the HF group was 4.2 (SD 1.3) which was similar to that for the men group who had the other

four CVD events. The medium value of eGFR for the HF group was 87.9 ml/min, which was also similar to the value of the combined group.

58.6% of HF men were obese, 22.0%, 20.0% and 0.5% were overweight, normal and underweight. The proportion of obese men having the other four CVD events was 21.6% lower than that of the HF men ($p<0.001$).

5.4.2.1.3 Comorbidities

In the HF group, the proportion of men having a history of diabetes was 26.6%, which was 4.2% higher than that of the four CVD events combined group ($p<0.001$). 49.4% of the men in the HF group had Hba1c test without diabetes, while the proportion was 46.3% in the four CVD events combined group ($p<0.001$). The average level of Hba1c was 41.2 mmol/mol (SD 10.6) in the HF group, which was similar to that in the four CVD events combined group ($p=0.003$). 98.5% of HF women with diabetes and the same proportion of diabetic women with the other four CVD events had Hba1c test. The average level of Hba1c was 68.0 mmol/mol in the HF group, which was 2.5 mmol/mol higher than that in the four CVD events combined group ($p=0.02$).

5.4.2.1.4 Medical history

10.2% of HF men had a family history of premature CVD, which was 3.1% lower than the proportion of men who had the other four CVD events with a family history of premature CVD ($p<0.001$). 9% of HF men had a history of atrial fibrillation, which was 3.7% in the men who had the other four CVD events ($p<0.001$). In terms of a history of cardiomyopathy, prosthesis or cardiac device implanted, and valve disease, the proportion of HF men having them was 1, 1.3 and 1.4, respectively, which was at least three times higher than that in the four CVD events combined groups ($p<0.001$).

5.4.2.1.5 Cardiometabolic medication

While 50.4% of HF patients having been dispensed antihypertensive medication and 28.1% of them having been dispensed antithrombotic medication, the differences in the proportion of men who had the other four CVD events using these two medications were 9.5% and 4.4%, respectively ($p<0.001$). 30.1% of men with HF had been dispensed lipid lowering medication

and the percentage was similar to men with the other four CVD events having been dispensed the same medication.

5.4.2.1.6 CVD risk score

The 5 year CVD risk for half of men who developed HF was at least 7.9% (IQR), while the median risk was 6.6% for the other CVD groups (IQR 6.7) ($p<0.001$)

5.4.2.2 HF group in comparison to each of the event group according to baseline characteristics

In male group, 10.4% had HF and CHD and non-cardiac fatal event took up the largest proportion which was 37.3% and 24.9% separately (Table 12).

Table 11 Baseline characteristics of men with HF comparing to men with each of event

Participants		**Male**							**p-value***
		Non-fatal CVD event					**Fatal event**		
		Heart failure	**Coronary heart disease**	**Cerebrovascular disease**	**Peripheral vascular disease**	**Haemorrhagic stroke**	**Cardiac**	**Non-cardiac**	
Participants (percentage of total cohort)		2,000 (10.4)	7,178 (37.3)	2,914 (15.2)	1,082 (5.6)	565 (2.9)	700 (3.6)	4,784 (24.9)	
Mean age, years (SD)		57.1 (10.7)	56.6 (9.6)	59.3 (9.5)	59.1 (9.6)	56.4 (10.2)	57.1 (9.9)	59.7 (9.6)	<0.001
Self-identified ethnicity, n (%)									<0.001
European	≥55 years	660 (55.1)	2,742 (65.4)	1,422 (70.2)	524 (69.6)	191 (59.1)	283 (66.3)	2,314 (68.4)	
	<55years	180 (22.4)	1,159 (38.8)	405 (45.7)	137 (41.6)	82 (33.9)	93 (34.1)	636 (45.4)	
Māori	≥55years	246 (20.5)	411 (9.8)	193 (9.5)	87 (11.6)	42 (13.0)	69 (16.2)	481 (14.2)	
	<55years	319 (40.0)	565 (18.9)	194 (21.9)	79 (24.0)	34 (14.1)	97 (35.5)	398 (28.4)	
Pacific	≥55years	222 (18.5)	465 (11.1)	202 (10.0)	90 (12.0)	44 (13.6)	57 (13.4)	361 (10.7)	
	<55years	271 (33.8)	704 (23.6)	185 (20.9)	85 (25.8)	75 (31.0)	67 (24.5)	262 (18.7)	
Chinese	≥55years	28 (2.3)	177 (4.2)	109 (5.4)	23 (3.1)	20 (6.2)	4 (0.9)	111 (3.3)	
	<55years	7 (0.9)	65 (2.2)	16 (1.8)	1 (0.3)	17 (7.0)	2 (0.7)	27 (1.9)	
Indian	≥55years	34 (2.8)	308 (7.3)	72 (3.6)	22 (2.9)	16 (5.0)	8 (1.9)	70 (2.1)	
	<55years	21 (2.6)	383 (12.8)	55 (6.2)	18 (5.5)	20 (8.3)	11 (4.0)	57 (4.1)	
Other Asian	≥55years	8 (0.7)	91 (2.2)	29 (1.4)	7 (0.9)	10 (3.1)	6 (1.4)	47 (1.4)	
	<55years	4 (0.5)	108 (3.6)	32 (3.6)	9 (2.7)	14 (5.8)	3 (1.1)	20 (1.4)	
NZDep quintile (%), n (%)									<0.001
1 (least deprived)		224 (11.2)	1,322 (18.4)	631 (21.7)	176 (16.3)	109 (19.3)	100 (14.3)	828 (17.3)	
2		274 (13.7)	1,306 (18.2)	545 (18.7)	160 (14.8)	88 (15.6)	102 (14.6)	778 (16.3)	
3		299 (15.0)	1,261 (17.6)	477 (16.4)	202 (18.7)	98 (17.4)	95 (13.6)	794 (16.6)	
4		394 (19.7)	1,468 (20.5)	549 (18.8)	202 (18.7)	123 (21.8)	157 (22.4)	974 (20.4)	
5 (most deprived)		809 (40.5)	1,821 (25.4)	712 (24.4)	342 (31.6)	147 (26.0)	246 (35.1)	1,410 (29.5)	
Smoking (%), n (%)									<0.001
Never smoker		1,004 (50.2)	4,222 (58.8)	1,707 (58.6)	451 (41.7)	333 (58.9)	345 (49.3)	2,368 (49.5)	
Ex-smoker		502 (25.1)	1,499 (20.9)	686 (23.5)	252 (23.3)	129 (22.8)	146 (20.9)	1,155 (24.1)	
Current smoker		494 (24.7)	1,457 (20.3)	521 (17.9)	379 (35.0)	103 (18.2)	209 (30.0)	1,261 (26.4)	
Mean SBP, mmHg (SD)		137.0 (16.8)	135.0 (16.2)	135.0 (16.2)	136.0 (16.1)	137.0 (17.4)	136.0 (17.1)	132.0 (15.9)	<0.001
Mean DBP, mmHg (SD)		83.0 (10.9)	82.0 (9.9)	82.0 (9.7)	81.0 (9.9)	85.0 (11.3)	84.0 (10.5)	80.0 (9.6)	<0.001
Mean TC/HDL (SD)		4.2 (1.3)	4.7 (1.3)	4.3 (1.3)	4.3 (1.3)	4.2 (1.3)	4.6 (1.4)	4.1 (1.3)	<0.001
eGFR (IQR), n (%)		87.9 (74.0-98.1)	87.0 (75.3-96.8)	85.0 (73.5-94.5)	85.0 (72.3-96.0)	86.7 (74.3-97.6)	88.2 (75.8-97.1)	88.1 (75.6-97.4)	<0.001
Missing value of eGFR, n (%)		312 (15.6)	1463 (20.4)	497 (17.1)	147 (13.6)	108 (19.1)	152 (21.7)	807 (16.9)	

		Non-fatal CVD event										Fatal event				p-value
		Heart failure		Coronary heart disease		Cerebrovascular disease		Peripheral vascular disease		Haemorrhagic stroke		Cardiac		Non-cardiac		
BMI, n (%)																<0.001
Underweight, BMI <18.5		10 (0.5)		21 (0.3)		11 (0.4)		9 (0.8)		3 (0.5)		7 (1.0)		59 (1.2)		
Normal weight, BMI 18.5-24.9		200 (10.0)		1,110 (15.5)		527 (18.1)		191 (17.7)		82 (14.5)		86 (12.3)		946 (19.8)		
Overweight, BMI 25.0-29.9		439 (22.0)		2,584 (36.0)		1,047 (35.9)		385 (35.6)		188 (33.3)		204 (29.1)		1,485 (31.0)		
Obese, BMI ≥30		1,172 (58.6)		2,749 (38.3)		995 (34.2)		388 (35.9)		210 (37.1)		287 (41.0)		1,397 (29.2)		
Missing value of BMI, n (%)		179 (9.0)		714 (10.0)		334 (11.5)		109 (10.1)		82 (14.5)		116 (16.6)		897 (18.8)		
Diabetes																
No, n (%)	Hba1c level available, n (%)	1,469 (73.5)	725 (49.4)	5,712 (79.6)	2,637 (46.2)	2,322 (79.7)	1,076 (46.3)	648 (60.0)	310 (47.8)	455 (80.5)	203 (44.6)	579 (82.7)	274 (47.3)	3,817 (79.8)	1,866 (48.9)	<0.001
	Hba1c mmol/mol (SD) (where available)		41.2 (10.6)		40.2 (8.9)		39.9 (9.2)		39.7 (5.1)		40.2 (12.0)		40.1 (11.7)		39.3 (8.3)	<0.001
Yes, n (%)	Hba1c level available, n (%)	531 (26.6)	523 (98.5)	1,466 (20.4)	1,442 (98.4)	592 (20.3)	585(98.8)	434 (40.1)	427 (98.4)	110 (19.5)	109 (99.0)	121 (17.3)	119 (97.5)	967 (20.2)	948 (98.0)	<0.001
	Hba1c mmol/mol (SD) (where available)		68.0 (23.9)		64.4 (20.6)		65.2 (21.6)		70.7 (25.8)		62.2 (19.7)		65.0 (20.8)		60.6 (20.8)	<0.001
Family history of premature CVD, n (%)		203 (10.2)		1,049 (14.6)		340 (11.7)		120 (11.1)		50 (8.9)		68 (9.7)		477 (10.0)		<0.001
History of atrial fibrillation, n (%)		179 (9.0)		199 (2.8)		163 (5.6)		44 (4.1)		25 (4.4)		20 (2.9)		165 (3.5)		<0.001
History of cardiomyopathy, n (%)		19 (1.0)		6 (0.1)		8 (0.3)		1 (0.1)		2 (0.4)		1 (0.1)		13 (0.3)		<0.001
History of cardiac valve prosthesis or device (ICD or pacemaker) implanted, n(%)		25 (1.3)		14 (0.2)		22 (0.8)		5 (0.5)		2 (0.4)		1 (0.1)		16 (0.3)		<0.001
History of valve disease, n (%)		27 (1.4)		13 (0.2)		16 (0.6)		3 (0.3)		3 (0.5)		0		9 (0.2)		<0.001
Medication at index assessment, n (%)																
Antihypertensive medication		1,007 (50.4)		2,742 (38.2)		1,252 (43.0)		565 (52.2)		243 (43.0)		286 (40.9)		1,669 (34.9)		<0.001
Antithrombotic medication		562 (28.1)		1,603 (22.3)		698 (24.0)		348 (32.2)		129 (22.8)		155 (22.1)		982 (20.5		<0.001
Lipid lowering medication		601 (30.1)		2,160 (30.1)		861 (30.0)		448 (41.4)		145 (25.7)		190 (27.1)		1,197 (25.0)		<0.001
Absolute 5-year CVD risk %, median (IQR)		7.9 (4.5-12.1)		6.2 (3.6-10.1)		7.1 (4.1-10.7)		8.8 (5.4-13.3)		6.1 (3.2-9.9)		7.2 (4.3-11.3)		7.1 (4.0-11.3)		<0.001

Note: BMI=body mass index; CVD=cardiovascular disease; DBP=diastolic blood pressure; eGFR=estimated glomerular filtration rate; Hba1c=haemoglobin A1C; HDL=high-density lipoprotein; IQR=interquartile range; N=number; NZDep=The New Zealand small-area index of relative socio-economic deprivation; SBP=systolic blood pressure; SD=standard deviation, TC=total cholesterol; *p for difference between men with HF and men with each of the other events.

5.4.2.2.1 Demographic factors

The mean age for men was similar to the mean age of those who were dead due to cardiac events, CHD and HS. On average, people who had PVD, Cevd and non-cardiac death were slightly older than those who had HF, with a mean age of 59.1 (SD 9.6), 59.3 (SD 9.5), and 59.7 (SD 9.6) ($p<0.001$).

While comparing the 55 and the over age group across outcome event groups, it can be seen that the proportion of European men in other event groups was at least 10% higher than that of the HF group, but similar to that of the HF group ($p<0.001$). However, the proportion of Māori men who had HF was all higher than that of the other outcome groups and particularly two times higher than that of the CHD and Cevd groups. Similarly, the proportion of Pacific men who had HF was all higher than that of other outcome groups ($P<0.001$). In the under 55 age group, the proportion of European men in other event groups was at least 10% higher than that of HF. In contrast, the proportion of Māori, Pacific, Indian and other Asians who had HF was all higher than that of the other outcome groups ($p<0.001$).

Compared to the HF group, there was a similar distribution of NZDep in the cardiac death group. Although the proportion of the HF men was higher than that of the other men who had other outcomes living in the most deprived areas, the difference between the proportion of HF group and that of Cevd group was 16.1%, which was the greatest and the difference between the proportion of HF group and that of cardiac death group was 5.4%, which was the smallest ($p<0.001$). For men who were grouped into the first and second quintile, those who had other outcomes all had a higher proportion than those who had HF. For men who were grouped into the third quintile, the proportion of those who had HF was only higher than that of those who had cardiac death (13.6%)($p<0.001$).

5.4.2.2.2 Societal factors and clinical characteristics

The percentage for HF men classified as current smokers was slightly higher than that of Cevd and HS men which took up 17.9% and 18.2%, respectively. However, it was 10.3% and 5.3% lower than that of people who had PVD and were dead due to cardiac events, respectively ($p<0.001$).

The mean SBP for HF men was similar to most of the groups except for the group who were dead due to non-cardiac event. While comparing the mean DBP and TC/HDL ratio across these event groups, the value was similar. This is the same case comparing the median value of eGFR across these event group expect for the Cevd group with an eGFR value of 85ml/min($p<0.001$). The distributions by BMI status for HF males was significantly different from that in other events groups, the proportion of obese males with HF was more than 20% higher than most of the groups except for the cardiac-death group which was 17.6% lower than that of the HF group ($p<0.001$).

5.4.2.2.3 Comorbidities

The proportion of HF men having diabetes was higher than most of the outcome groups but was lower than PVD group which had 40.1% of patients having diabetes ($p<0.001$). The proportion of men having Hba1c test without diabetes was the highest in the HF group compared to that of other outcome groups and the Hba1c level was similar across these seven groups ($p<0.001$). In contrast, the average level of Hba1c for HF men having diabetes was 2.0-7.4 mmol/mol higher than most of the event groups except for the PVD group which was 70.7mmol/mol ($p<0.001$).

5.4.2.2.4 Medical history

The proportion of HF men having a family history of premature was 4.6% lower than that of CHD men but similar to other CVD group. The proportion of HF men with a history of atrial fibrillation was at least approximately two times higher than that of other event groups ($p<0.001$). In terms of the proportion of patients having a history of cardiomyopathy, prosthesis or cardiac device implanted or valve disease, the value in the HF group was overall at least almost two times higher than that in the other groups ($p<0.001$).

5.4.2.2.5 Cardiometabolic medication

50.4% of HF men had been dispensed antihypertensive medication, which was more frequent than other groups except for PVD patients (52.2%) ($p<0.001$). 28.1% of HF patients used antithrombotic medication and this was more than 5% higher than other groups except for the PVD group where 32.2% were dispensed antithrombotic medication ($p<0.001$). The proportion of HF men who had been dispensed lipid lowering medication was similar to that of men with

CHD, Cevd and cardiac fatal event but 11.3% lower than that of men with PVD and 5% higher than that of men with HS and a non-cardiac fatal event ($p<0.001$).

5.4.2.2.6 CVD risk score

The median 5-year CVD risk for men who developed HF was 7.9% (IQR 7.6), which was 0.7-1.1% riskier than most of the groups. However, for the PVD group, they would have an 8.8% risk of developing CVD event within the next five years.

5.5 The proportion of heart failure patients who had CHD-related subsequent admissions within a year

After their first CVD admission, the participants who had HF as their first CVD continued to be followed until June 2021. Out of 3,505 participants who had HF as their first CVD event, 2096 (59.8%) were readmitted again within one year, of which 945 (26.9%) were due to CVD events. Out of 945 patients, 143 (4.1%) were readmitted with CHD recorded as either their principal diagnosis or secondary diagnosis. As the denominator is the number of patients who had HF as their first CVD event (3,505) and the numerator is the number of patients who had HF as their first CVD event and had readmission within a year due to CHD (143), the proportion is 4.1%.

Table 13 depicts the number of patients who were readmitted within a year due to CHD by the times of admission. The majority of patients were readmitted only once within a year while 9.1% had two admissions a year due to CHD.

Table 12 The times of admission due to CHD in patients with HF

Times of admission[a]	Number of patients (N=143), n (%)
1	128 (89.5)
2	13 (9.1)
3	1 (0.7)
4	1 (0.7)

Note: CHD= coronary heart disease, CVD=cardiovascular disease, HF=heart failure,

[a] = times of admission related to CHD within a year after having their first CVD hospitalization due to HF.

5.6 Summary of chapter 5

By analysing the PREDICT data, this chapter fulfilled three objectives including describing the characteristics of HF patients whose first presentation to hospital for CVD is due to HF, comparing the characteristics of patients who had HF as their first CVD event with those who had other atherosclerotic disease, haemorrhagic stroke or cardiac fatal event as their first CVD event and estimating the proportion of HF patients who had CHD-related subsequent admissions within a year. Additionally, the baseline characteristics of the entire PREDICT cohort by sex and the comparison of baseline characteristics between CVD and non-CVD group by sex was given.

410,812 PREDCIT participants were included as the denominator of the cohort and there were 179,435 (43.7%) women and 231,386 (56.3%) men. 8,452 women had the first presentation of CVD, within which 1,505 (12.4%) of the presentations were due to HF. 14,439 men had the first presentation of CVD, within which 2,000 (10.4%) were due to HF. Participants whose first CVD presentation was due to HF were then compared to participants whose first CVD presentation was due to another CVD event based on their baseline characteristics including demographic factors, societal factors, clinical characteristics, medical history, cardiometabolic medication, and CVD risk score by sex. The important findings were demonstrated. Women with HF tended to be Māori and Pacific, living in the most deprived areas, being obese (BMI ≥30), having a higher prevalence of diabetes and having a history of AF, valve disease and cardiac valve prosthesis or device (ICD or pacemaker) implanted. In the 55 and over age group, the proportion of both Māori and Pacific women with HF was 21.3% and 20.6% separately which was nearly 10% higher than that of other non-fatal CVD event ($p<0.001$). Similarly, in the under 55 age group, the proportion of Pacific women with HF was 42.8% which was 9% to 22% higher than that of other CVD events ($p<0.001$). Women with HF tended to live in the most deprived areas compared to women with other CVD and the proportion differences was nearly 10% ($p<0.001$). 60.7% of women with HF had BMI≥30, which was 20-25% higher than that of women with any of the other CVD events who had BMI≥30 ($p<0.001$). Women with HF had a higher prevalence of diabetes (30%) and a slightly higher average level of Hba1c compared to patients with other CVD events except for PVD (36.2%) ($p<0.001$). 7% of women with HF had a history of AF, 1% had a cardiac valve prosthesis or device (ICD or pacemaker) implanted and 1.5% had valve disease, which was two to three times higher than women with any of other CVD events ($p<0.001$).

Regarding to the findings about men with HF, it was found that compared to men with other CVD, men with FH tended to be Māori and Pacific, living in the most deprived areas, being obese (BMI ≥30), with a higher prevalence of diabetes and having a history of AF, cardiomyopathy, valve disease and cardiac valve prosthesis or device (ICD or pacemaker) implanted. The proportion of Māori and Pacific men with HF was 20.5% and 18.5%, respectively, in the 55 and above age group and 40% and 33.8%, respectively, in the under 55 age group, which were all higher than that of any other CVD groups and the differences could be ranging from 5 to 21% ($p<0.001$). The differences in proportion can be 15% higher comparing men with HF who lived in the most deprived areas to other CVD patients living in the most deprived area ($p<0.001$). Nearly three fifths men with HF had BMI≥30, which was more than one fifth higher than the proportion of men with other non-fatal CVD event and 18% higher than the proportion of patients with fatal CVD event ($p<0.001$). The proportion of men with diabetes was 26.6% in HF group, which was around 6% higher than that of the other CVD group except for the PVD group which was 40.1% ($p<0.001$). Similarly, the HF group with diabetes had the highest value of Hba1c (68 mmol/mol) among all CVD event groups except for the PVD group which was 70.7 mmol/mol ($p<0.001$). Men with HF had the highest prevalence of AF at 9%, cardiomyopathy at 1%, cardiac valve prosthesis or cardiac device (ICD or pacemaker) implanted at 1.3% and valve disease at 1.4% among all CVD groups. The proportion of men with HF having a medical history as mentioned above can be at least two times higher than men with any of the CVD events ($p<0.001$).

In terms of the readmission cause, the proportion of HF patients who had CHD-related subsequent admissions within a year was 4.1%.

6 Chapter 6. Discussion

While the last chapter presents the findings from the analysis of the PREDICT data, this chapter contains the summary of the key findings from the PREDICT data and compares these with the findings of the scoping review. The findings in terms of the thesis's hypotheses are also discussed in this chapter. In addition, the strengths and limitations of the thesis, its implications for the health sector and future research are explored.

Due to the presence of the sex chromosomes, the most fundamental genetic level is different in the bodies of the different sexes (132). There is robust evidence showing the diverse underlying mechanism of CVD comparing patients of different sexes (133)(134). For instance, vascular physiology can be impacted by oestrogens and androgens, as premenopausal women appear to be less likely to have CVD and CVD related risk factors especially CHD and hypertension compared with their age cohort men, until the occurrence of menopause (133). Therefore, considering the sex differences in CVD, each sex has been viewed separately in this thesis.

6.1 Summary of key findings from the PREDICT data

6.1.1 Women who develop heart failure compared to the separate non-heart failure CVD group according to baseline characteristics

There were statistically significant differences in the baseline characteristics except for the history of cardiomyopathy that could be observed comparing women whose first presentation of CVD was due to HF and women with CHD, Cevd, PVD, HS or CVD fatal event.

The differences by ethnicity were stand out. Māori and Pacific women who were aged 55 and above and Pacific women who were aged under 55 were more likely to be affected by HF than any of other CVD events. In the 55 and over age group, the proportion of both Māori and Pacific women with HF was 21.3% and 20.6% separately which was nearly 10% higher than that of other non-fatal CVD event ($p<0.001$). Similarly, in the under 55 age group, the proportion of Pacific women with HF was 42.8% which was 9% to 22% higher than that of other CVD events ($p<0.001$).

Regarding the NZDep index, women with HF tended to live in the most deprived areas compared with patients with any of other CVD events as the proportional differences were

nearly 10% comparing the proportion of women with HF living in the most deprived areas (42.1%) with that of women with other CVD living in the most deprived areas ($p<0.001$).

The proportion differences in terms of BMI was significant, 60.7% of women with HF had BMI≥30, which was 20-25% higher than that of women with any of other CVD events who had BMI≥30 ($p<0.001$).

In terms of diabetes, women with HF had a higher prevalence of diabetes (30%) and a slightly higher average level of Hba1c compared to patients with other CVD events except for PVD (36.2%) ($p<0.001$). Similarly, the average level of Hba1c in women with HF who had no diabetes was 41.4 mmol/mol, which was approximately 1 mmol/mol higher than that of other CVD groups without diabetes ($p<0.001$).

Regarding the medical history, 7% of women with HF had a history of AF, 1% had a cardiac valve prosthesis or a device (ICD or pacemaker) implanted and 1.5% had valve disease, which was two to three times higher than women with any of the other CVD events ($p<0.001$).

The dispensing of antihypertensive and antithrombotic medication was high in women with HF as compared to women with other CVD events.

6.1.2 Men who develop heart failure compared to the separate non-heart failure CVD group according to baseline characteristics

The statistically significant differences in baseline characteristics could be observed comparing men with HF as their first CVD presentation and male patients with CHD, Cevd, PVD, HS or a CVD fatal event.

Regardless of the age range, the differences by ethnicity were significant. The proportion of Māori and Pacific men with HF was 20.5% and 18.5%, respectively, in the 55 and above age group and 40% and 33.8%, respectively, in the under 55 age group, which were all higher than that of any other CVD groups and the differences could range from 5 to 21% ($p<0.001$).

A high proportion of men with HF living in the most deprived area was found (40.5%) and the differences in proportion can be as 15% higher comparing men with HF who lived in the most deprived area to other CVD patients living in the most deprived area ($p<0.001$).

Men with HF tended to be obese. The difference was significant by BMI as nearly three fifths of the men with HF had a BMI≥30, which was more than one fifth higher than the proportion of men with other non-fatal CVD events and 18% higher than the proportion of patients with a fatal CVD event ($p<0.001$).

The proportion of men with diabetes was 26.6% in the HF group, which was around 6% higher than that of the other CVD group except for the PVD group which was 40.1% ($p<0.001$). Similarly, the HF group with diabetes had the highest value of Hba1c (68 mmol/mol) among all CVD event groups except for the PVD group which was 70.7 mmol/mol ($p<0.001$).

Men with HF had the highest prevalence of AF at 9%, cardiomyopathy at 1%, cardiac valve prosthesis or cardiac device (ICD or pacemaker) implanted at 1.3% and valve disease at 1.4% among all CVD groups. The proportion of men with HF with a medical history mentioned above can be at least two times higher than men with any of the CVD events ($p<0.001$).

Patients with HF had a higher proportion of cardiometabolic medication in terms of antihypertensive and antithrombotic medication dispensed as compared to patients with other CVD except for PVD.

6.1.3 The readmission pattern

Out of 3,505 participants who had HF as their first CVD event, 2096 (59.8%) were readmitted again within one year, of which 945 (26.9%) were due to CVD events. Out of 945 patients, 143 (4.1%) were readmitted with CHD recorded as either the principal diagnosis or a secondary diagnosis. Among these 143 patients, the majority of patients (89.5%) were readmitted only once within a year while 9.1% of them had two admissions a year due to CHD.

6.2 Answers to hypotheses

Hypothesis testing for hypothesis 1 and hypothesis 2 were established based on the key findings from the population-based New Zealand study. The two hypotheses are briefly summarised below.

-Hypothesis 1: There are differences between people who developed HF as their first CVD event and people who developed other CVD

-Hypothesis 2: People whose first CVD event as HF may represent a group of people who have undiagnosed CHD

For hypothesis 1, it can be seen that regardless of sex, while comparing the baseline characteristics of patients who developed HF as their first CVD event to people who developed other CVD, the differences by ethnicity, NZDep, and BMI were significant and the difference by medical history including AF, valve disease, cardiomyopathy, and cardiac valve prosthesis or device (ICD and pacemaker) were also noticeable. The higher proportion of HF people having BMI≥30 and having the medical history mentioned above most likely reflects that each type of CVD has different pathological processes and CVD risk factors might affect the manifestations of CVD in different ways. The differences by ethnicity and NZDep might suggest the various societal factors and potentially genetic background associated with each ethnic and socio-economic group.

For hypothesis 2, our results reject it as the proportion of HF patients who had subsequent admission of CHD within a year was unexpectedly low (4.1%). However, although HF can be commonly developed by ischemic causes which are normally attributed to CHD, non-ischemic causes can also contribute to the pathophysiological process of HF (135,136). Non-ischemic HF is any form of HF which has not resulted from the obstructive coronary atherosclerosis that limits blood flow and non-ischemic causes, this can include hypertensive heart disease, valve disease, cardiomyopathy and cardiac dysfunction, including dysfunction stimulated by arrhythmias, such as rapid AF (136)(137).

It can be observed from the findings of hypothesis 1 that while comparing baseline characteristics in terms of history of AF, cardiomyopathy, and valve disease, people who had HF as their first presentation of CVD had a several times higher proportion than people who

had other CVD. In addition, the proportion of obese people with HF (BMI≥30) was noticeably higher than that of people with other CVD.

It is important to understand that obesity can be related to non-CHD causes of HF (28). For instance, obesity can lead to the structural changes of the heart as excess adipose tissue increases metabolic demands and thus hyperdynamic circulation, increased blood pressure and stress on the heart, which can lead to HF (28). Obesity can also cause changes related to the left ventricular such as LVH, which can lead to LV dilatation and thus result in HF (28)(138). Obesity can also be associated with other non-CHD causes of HF, such as arrhythmias and cardiac valve disease. For example, the cardiac repolarisation can be impacted in obese people due to the increased plasma catecholamine levels which directly results in the elevated free fatty acid levels and increased plasma catecholamine levels can also lead to the decreased threshold for arrhythmias (28). Hence, obesity can contribute to the abnormalities in cardiac conduction and arrhythmias. Furthermore, chronic inflammation as a well-known characteristic of obesity can result in the increase of inflammatory mediators which can differentiate valve interstitial cells into osteoblasts and thus the occurrence of calcification in valve leaflets. This shows how obesity can be a risk factor for cardiac valve disease (138). The examples above demonstrate the relationship between obesity and the non-CHD cause of HF.

Hence, the findings of hypothesis 1 that people whose first CVD presentation was due to HF had a higher proportion of medical history including AF, cardiac valve disease and cardiomyopathy than people with other CVD and the proportion of obese people with HF (BMI≥30) is discernibly higher than that of people with other CVD and might imply that non-CHD causes could take up a certain part of the causes for people who did not have a previous history of CVD to develop HF. This might provide a potential reason for the finding of hypothesis 2 that the proportion of HF patients who had subsequent admission of CHD within a year was low (4.1%).

However, this thesis did not analyse the pattern of readmission which was related to the non-ischemic causes in people who had HF as their first presentation of CVD. This can be further investigated.

While there are various aetiological factors of HF including CHD, hypertension, cardiomyopathy and AF, the predominant factors that affect HF can be different among

countries (16). In the developed countries, HF factors are commonly caused by CHD and hypertension, whereas cardiac valve and cardiomyopathy are the primarily causes of HF in the developing countries (16). In NZ, although there was an increase of HF incidence with non-ischaemic aetiology from 2006 to 2018 , the dominant causative factors that cause HF were still CHD and AF in 2018 (13). Nevertheless, it is worth noticing that in the study conducted by Chan et al., the causative factors were determined based on the codes of comorbidities at the time of incident HF hospitalisation, which means that it could be difficult to investigate whether AF was the cause or the consequence of HF (13). In the context of increasing level of obesity, not much has been known about the relationship between obesity in terms of BMI measurements and the non-CHD risk factors of HF in NZ.

6.3 Comparison with studies from scoping review and other relevant studies

In order to test the hypotheses, the differences of CVD risk profiles between the HF group and the other CVD group and how much the causes of their HF presentation are associated with CHD were examined not only based on the New Zealand data but also the previously published articles included in the scoping review and in other relevant studies. According to the key baseline characteristics, the comparisons between the findings of analyses of the PREDICT cohort and the findings of articles from the scoping review and other relevant studies were developed.

6.3.1 Difference by ethnicity

The major differences in the proportion of patient with different CVD events by ethnicity that were found in this study are comparable to previous findings from the MESA study in the US (81), though differs from findings of a relevant study from the CALIBER dataset in the UK (139). Unlike this study, the MESA study focused on races including African American, Caucasian, Chinese American and Hispanic and compared patients with HF as their initial presentation of CVD event to patients with CHD as their initial presentation of CVD event. while the CALIBER study focused on ethnicities including White, Black and South Asian and compared patients with HF as their initial presentation of CVD event to patients with the other 11 most common CVD as their initial presentation event CVD. The clear differences in the ethnic profile of HF in comparison to CHD were found in the MESA study where a significant higher proportion of African American had HF. In contrast, the CALIBER study showed no ethnic differences in patients with HF.

This CALIBER study which was established to study the cohort with initial presentation of CVD in the England with patients recruited from the English CPRD practices and linked across different clinical data sources (140) demonstrated the similar rates of hypertension between the Black patients and the White patients (139). However, according to the UK population data, Black groups have a higher prevalence of hypertension compared to the White groups, which can indicate the potential selection bias in CALIBER study (141) Also, in the CALIBER study, the self-identified ethnicity was defined from the CPRD and EHS database, but a significant number of patients had no record of ethnicity. These people were thus excluded from the study and they accounted for 43.6% of the eligible study population (139). Except for the selection bias which might impact on their results, the way they broadly categorised ethnic group might also conceal the ethnic differences in different CVD groups (139).

Although this thesis did not analyse differences in CVD risk factors by ethnicity, a NZ study which also used the PREDICT cohort showed that among all ethnic groups including European, Māori, Pacific, Indian and other Asian, Māori had the highest prevalence of hypertension and AF while Pacific had the highest prevalence of diabetes and highest proportion of obese people (54). This might be able to explain the ethnic variations between heart failure and other CVD events. Also, according to the latest Māori Health Chart Book and Pacific Health Chart Book, the proportion of Māori and Pacific living in the higher neighbourhood deprivation was significant comparing to that of other ethnic groups (142,143). The finding of this thesis that patients with HF were more likely living in the most deprived areas compared to patients with other CVD, which might also be relevant to the ethnic differences noticed.

However, it is worth noting that with the data of ethnicity being nearly complete (>99%) in the PREDICT dataset, the proportions of ethnic groups from PREDICT differed from those from the NZ 2018 Census as the proportion of Pacific people was approximately doubled compared with the national Census (144). This is due to the facts that first, the PREDICT cohort was selected predominantly from the northern region of New Zealand where 65% of Pacific people live (145); second, Pasifika as well as Māori and Indian ethnicities are considered as risk factors for CVD, hence the recommended age to have CVD risk assessment for these groups is 10 years earlier than other ethnic groups (4). These can influence the statistical significance of the ethnic differences found by the CVD group.

6.3.2 Difference by socioeconomic deprivation

This study found that the proportion of people with HF was the highest among all CVD groups living in the most deprived area. It is partially consistent with the finding from a relevant study from CALIBER dataset where female patients with HF living in the most deprived area had the highest proportion in comparison to that of women with other CVD (146) However, in the male group, this study found that the association between PVD and the fifth quintile of deprivation (most deprived) was stronger than the association between HF and the fifth quintile of deprivation, which was different from the findings of this study (146).

This CALIBER study used the UK index of multiple deprivation (IMD) to measure the level of socioeconomic deprivation (146). Although there are differences in the input measures and the weights allocated to each input measure between UK IMD and NZ IMD, which was developed based on the UK IMD, they are similar enough to be compared (147) . While this study used NZDep instead of IMD as a measurements of deprivation, a study which compared New Zealand IMD indexes with NZDep showed that their way of ranking small areas and their associations with health outcomes were similar (147). Considering that the CALIBER study used four different data sources to define HF and other CVD health outcome, the differences in findings might be caused by errors of these databases. Also, the CALIBER study involved primary care cases which could have a different level of severity from hospitalised cases and it was reported that the association with socioeconomic deprivation could be stronger if primary care cases were excluded (146).

6.3.3 Difference by BMI status

It was found in this study that the proportion of people with HF who were obese (BMI≥30) was highest among CVD subtypes. Similarly, one study from the scoping review found that the initial presentation of HF had the most robust association with higher BMI among CVD subtypes including CHD and stroke (87). Another article from the MESA study also reported BMI by comparing HF with CHD. This MESA defined BMI through physical examination conducted by trained staff and defined HF through a medical records review (81). Nevertheless, it did not provide the proportion of obese people in each group but provide the mean BMI and showed that the difference in mean BMI score between patients with HF and patients with CHD was statistically significant but it was clinically unimportant (28.6 in comparison to 28.3)(81).

6.3.4 Difference by diabetes status

The proportion of HF patients with diabetes was lower than that of PVD patients but higher than that of other CVD patients. This finding is consistent with two studies from the scoping review. In the MESA study, which only compared HF and CHD, the higher proportion of HF patients with diabetes was found (81). Similarly, in the relevant study from the CALIBER dataset, it showed that while the association between diabetes and PVD was strongest among the 12 most common CVD diseases, the association between diabetes and HF was the second strongest association (91). Although the results of the CALIBER study came from analysis which involved the primary care data, it was reported that if those primary care data were excluded, the only difference was the slightly stronger association between diabetes and HF (91).

6.3.5 Difference by other characteristics

Regarding the cardiometabolic medication, only one study from the scoping review reported the comparison between the proportion of hypertension medication usage in HF group and CHD group and the finding was comparable to the finding of this thesis (81). In terms of other characteristics such as the history of AF and cardiomyopathy, no study from the scoping review or other revelant studies that reported relevant findings.

6.3.6 The readmission pattern

While this thesis found a low CHD-related readmission rate (4.1%) within a year among patients whose first CVD event was HF, there was no study from the scoping review reporting the readmission pattern for HF patients. Nevertheless, an NZ study showed that more than one quarter of the causes for the incident HF hospitalisation was due to CHD, which implies that the CHD-related readmission proportion estimated by this study is quite low (13). It is worth noticing that the prioritisation method used in this thesis was to prioritise CHD and then HF when multiple CVD events occurred during a single admission, which might contribute to the unexpected result in terms of the CHD-related readmission proportion.

6.3.7 Strengths and limitations of this thesis

This thesis demonstrates a number of strengths. First, the data was predominantly collected from the CVD risk assessments conducted by health professionals in primary care, which increased the accuracy of the data compared with the method that relied on secondary data.

With the supplementary information from regional and national databases including hospitalisation in private hospitals, the comprehensive and complete aspect of the data was also increased. Secondly, the PREDICT cohort is large, contemporary and ethnically diverse. With the large size, CVD events can be divided into multiple groups within the same sample, so the study can be sufficiently powered to examine the differences between HF and other CVD. Thirdly, the PREICT cohort is likely to be representative of the New Zealand population who have no previous CVD and are recommended for CVD risk, as more than a third of all primary care practices in New Zealand were involved in the quantitative analysis and eligible patients included in the analysis that could reach to approximately 90%. Fourthly, a comprehensive scoping review incorporated in this thesis can inform a discussion of how the data provenance could impact on the findings of the results, which has not always been recognised in the way research is interpreted. Finally, comprehensive comparisons were carried out in terms of demographic characteristics and clinical risk factors, which can be expanded upon by further study that could validate the pathophysiological process of HF and add onto the evidence base related to the prevention of HF in different subpopulations.

This thesis also has some limitations. First of all, although data-linkage is a powerful method to assess event rates on a large scale, using hospital coding solely might introduce misclassification bias if the validity of CVD and HF coding is not reasonable enough. This quantitative analysis exclusively relied on ICD-coded diagnoses to define targeted health outcomes during follow up for analysis. Nevertheless, HF diagnoses defined by ICD-10 in administrative data sets have been validated with reasonably high accuracy (73) In addition, relevant diagnoses were less likely to be missed as the CVD definition of this thesis was broad. Second of all, the prioritised method applied in this thesis was to prioritise CHD and then HF if multiple CVD events occurred during a single admission, which means if a first presentation for CVD included any type of coronary heart disease, this was prioritised ahead of HF during the same admission. Although this method was in alignment with the coding practices of the VIEW programme, the study findings of this thesis might be impacted. Third of all, not all non-fatal CVD and HF events can be captured, as some people will be diagnosed exclusively in the primary healthcare sector which are not coded in the national routine health databases. Nevertheless, events detected from hospitalised cases could be considered as the most definitive CVD diagnoses as they are more likely to be accurate in comparison to the diagnoses made in the primary care or they tend to be severe enough to reach the threshold for hospitalisation or result in death. Finally, BMI data and eGFR data were missing in 16.4% and

20.9% of the study population, respectively. However, the missing mechanism depends neither on observed data nor on the missing data. This means that there were no significant differences between the proportion of participants with BMI having HF (0.23%) and the proportion participants with a BMI missing value (0.26%) having HF and the proportion of participants with eGFR having HF and the proportion of participants without eGFR having HF was the same at 0.2%. In addition, the missingness of BMI value was not related to the missingness of eGFR value because the proportion of people with both BMI and eGFR missing was similar to the proportion of people with BMI data but eGFR missing (21.4% vs 20.8%) and it was also similar to the proportion of people with eGFR but BMI missing (16.8% vs 16.3%). Hence, although the missingness of BMI and eGFR data might cause standard errors large through reducing the sample size but it did not introduce a systematic error (148).

6.3.8 Implications of study for the heath sector

The results of this study have important implications for HF prevention. In New Zealand, there are many ways that are promoted to prevent CVD at the population strategy level. For example, the smokefree environments legislation supports behaviour change in terms of smoking cessation (6). Given the result that people who had HF as their first CVD event differed significantly in their BMI status from people who had other CVD, it is underscored that the strategies for managing obesity should be emphasised. In order to tackle the obesogenic environment, the NZ government is acting in various ways (149). For instance, the Healthy Active Learning aims to encourage and enhance healthy eating behaviours and physical activity by providing new resources for health and physical education curriculum and putting healthy food and water-only policies in place in all schools across NZ (150). Also, the National Healthy Food and Drink Policy is put in place for Health New Zealand (previously district health boards) to make the work and public places healthy food environments (149). In terms of promoting physical activity, Sport New Zealand is working on policies and implementing policies to promote walking, cycling, sport and active recreation as a way to respond to the World Health Organization's Global Action Plan on Physical Activity (35,149) Furthermore, with the aim of improving BMI measurement and monitoring BMI, the Clinical Guidelines for Weight Management in New Zealand Children and Young People is implemented in primary care and Well Child providers (151). The actions mentioned above demonstrate the importance of multi-organisational approaches in addressing obesity. Other actions implementing on the energy-dense food environment related to the industries should also be emphasised. For example, food

labelling should be improved because labelling of food ingredients, such as trans-fat acid which can increase weight gain is not mandatory, in most of the cases. unless there is a nutrition content claim about cholesterol or saturated, polyunsaturated, monounsaturated fats, or trans-fatty acids or omega-3, omega-6 or omega-9 fatty acids (152). Therefore, in order to tackle the obesogenic environment to prevent HF in NZ, it is critical to monitor the progress of policies put in place and implementing polices to regulate food industries.

With the prevalence of obesity risking steadily, the trends in HF event rates are likely to impacted negatively. If this is the case, risk-based strategy to prevent HF will become progressively critical (4). At the individual level, CVD risk assessment is recommended based on the New Zealand guidelines for people who are at certain ages according to their sex and ethnicity and by investigating their CVD risk factors, certain recommendations will be provided for people at risk(12). According to the latest version of primary prevention equations which have been implemented in primary health care, BMI has been included as a required variable(65). This will increase capture of BMI and add focus on BMI as an independent risk factor for CVD risk. However, considering the higher proportion of non-ischemic causes of HF in patients with HF in comparison to patients with other CVD and the low proportion in people with HF who subsequently present with CHD, the current CVD risk assessment could be strengthened through adding non-ischemic causes of HF including cardiomyopathy and cardiac valve disease for the better prevention of HF. This suggestion is supported with the convenient measuring method of these variables, as the presence of these factors can be easily obtained from the medical record or the patient with yes/no answers.

Given the differences by ethnicity found in this study, the HF inequities are evident among Māori and Pacific. It can be seen from the study findings that Māori and Pacific people are bearing greater burdens of HF outcomes than other ethnic groups. Although the priorities are given to the Māori, Pacific and South Asian people for CVD risk assessment as they are recommended to be screened for CVD at a younger age than other ethnicities (9), other interventions should be implemented to reduce inequities in exposure to HF risk factors and outcome for Māori and Pacific people.

With the purpose of providing public service, the Ministry of Health is responsible for contributing to the Crown fulfilling its obligations under Te Tiriti o Waitangi which is framed by principles including equity and active protection(153). Whakamaua: Māori Health Action

Plan 2020-2025 has been developed and underpinned by Tiriti obligations to guide government's direction for advancing Māori health (154). One of the important objectives is to make sure that Iwi, hapū, whānau and Māori communities can exercise their authority to enhance their health status and wellbeing, which has been responded well by the Pae Ora Act(154,155). One of the new entities established by the Pae Ora (Healthy Futures) Act, is the Māori Health Authority which will be working as an independent statutory authority to promote Māori health by responding to the needs of Māori (155). Another important objective of Whakamaua is to reduce health inequities and health loss of Māori by influencing the way NZ's health and disability system operates, for instance, giving priorities to equitable access to services and outcomes for Māori (154). It is critical to monitor the progression of these objectives, for example, given that HF is affecting Māori disproportionately, the comparison for the rate of HF between Māori and non-Māori/non-Pacific should be tracked on a regular basis.

In terms of reducing health inequities for Pacific, Ola Manuia: The Pacific Health and Wellbeing Action Plan 2020-2025 was established as a guide to support Pacific people's health and achieve health equity (156). Interventions that are likely to reduce inequities include empowering Pacific through increasing their knowledge and understanding of how to manage their health and changing the way health sector operates. The prevalence and incidence of HF should also be measured regularly to make sure that the strategies in progressing towards the outcomes (156).

In terms of socio-economic status (SES), the result that people living in the most deprived area were prone to have HF than other CVD implicates that interventions aiming at health issues related to SES should be put in place to prevent HF. Firstly, the health sector should understand the importance of socioeconomic status as a driver of health outcomes. Income, education, employment and housing are the key variables of SES, which influence the way people grow, work and live and can therefore have an critical impact on health inequities(157). SES can mediate a person's ability of accessing healthcare. Access to health services suggests relevant public health services and the availability of providers, physically accessible and affordable services, and acceptable, culturally appropriate services and providers respecting medical ethics (158). For people with high SES, barriers to care can include costs related issues, such as appointment cost, transportation, medication, and lost employment time, low health literacy and provided-related barriers, such as cultural misunderstandings (159). The health system can

enforce the legislation and regulations, establish policies or reallocate resources to reduce barriers for these patients. For example, considering the location of primary health care services to remove the barrier of lacking transport (159). Finally, the health service access and quality and outcomes by SES should be monitored and actions should be implemented if inequalities persist.

6.4 Recommendations for future research

This thesis has explored the different methods of defining HF and baseline characteristics through a comprehensive scoping review. Clearly, the findings can be conditional on the type of data analysed, which underscores the importance of recognising data provenance while interpreting the results of the study or comparing results between different studies. Hence, for future research, data provenance and how it might impact on the finding derived is recommended to be discussed.

As this quantitative analysis solely used the ICD-10-AM code to define HF and other health outcomes and this quantitative analysis prioritised CHD before HF while identifying health outcomes from multiple CVD events occurred during a single admission, the ability to use this approach to answer the hypothesis 2 might have been undermined. Although the findings of hypothesis 1 might imply the findings of hypothesis 2 to a certain degree, it is recommended that a different type of data can be used to test the hypothesis, which means that HF can be prioritised before another CVD event and medical chart review can be used as a supplementary method and primary care data can be involved so that milder HF cases could also be captured for analysis.

The findings on differences in baseline characteristics while comparing people who had HF as their first CVD and people who had other CVD are a new finding for the New Zealand literature. Given the higher proportion found in HF patients with certain characteristics including being Māori and Pacific, living in the most deprived area and many of whom are obese, there is potential to further compare the association of these characteristics with HF and other CVD after adjusting for traditional CVD mediators. Further research to understand better the association between ethnicity and HF might help improve HF prevention among Māori and Pacific people and thus achieving equity of HF in New Zealand. Also, the finding that Māori and Pacific people with HF took up the largest proportion in the younger aged group implicates

that further research should investigate the interplay between ethnicity and age to provide explanations for this difference.

Although this thesis has presented that most people whose first CVD event as HF did not have CHD-related readmissions within a year, a more precise analysis of the readmission pattern should be conducted. Non-ischemic causes, such as valve disease, cardiomyopathy should be investigated while analysing the readmission pattern. Also, the relationship between non-ischemic causes of HF and obesity should be better explored so the understanding of HF aetiology can be enhanced.

Reference list

1. Roger VL. Epidemiology of Heart Failure. Circ Res [Internet]. 2021[cited 2021 Sep 18];128(10):1421–34. Available from https://www.ahajournals.org/doi/10.1161/CIRCRESAHA.121.318172

2. Lippi G, Sanchis-Gomar F. Global epidemiology and future trends of heart failure. AME [Internet]. 2020 Jun 25 [cited 2022 Feb 18];5(15). Available from: https://amj.amegroups.com/article/view/5475

3. Chan ZL, Kerr AJ, Doughty RN. Temporal trends in the burden of heart failure. Intern. Med. J [Internet]. 2021;51(8):1212-8. Available from http://onlinelibrary.wiley.com/doi/abs/10.1111/imj.15253

4. New Zealand Guidelines Group, National Heart Foundation of New Zealand. The assessment and management of cardiovascular risk. [Internet]. Wellington (NZ): New Zealand Guidelines Group; 2018 [cited 2022 Feb 1]. Available from: https://www.health.govt.nz/system/files/documents/publications/cardiovascular-disease-risk-assessment-management-primary-care-feb18-v4_0.pdf

5. Blakely T, Kvizhinadze G, Atkinson J, Dieleman J, Clarke P. Health system costs for individual and comorbid noncommunicable diseases: An analysis of publicly funded health events from New Zealand. PLoS Medicine [Internet]. 2019 Jan 8;16(1):e1002716. Available from https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002716

6. Chan ZL, Kerr A, Grey C, Selak V, Lee MAW, Lund M, et al. Contrasting trends in heart failure incidence in younger and older New Zealanders, 2006–2018. Heart. 2022 Feb 1;108(4):300–6.

7. Lala A, Desai AS. The Role of Coronary Artery Disease in Heart Failure. Heart Fail Clin. [Internet]. 2020. [cited 2021 Aug 30]. Available from: https://www-clinicalkey-com-au.ezproxy.auckland.ac.nz/#!/content/playContent/1-s2.0-S155171361300113X?scrollTo=%23hl0000241

8. Khan H, Kalogeropoulos AP, Zannad F, Marti CN, Wilson PW, Georgiopoulou VV, et al. Incident Heart Failure in Relation to Vascular Disease. Eur J Heart Fail. [Internet] 2014 May;16(5):526–34. Availabel from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4648241/

9. Ministry of Health. Smokefree Environments Legislation [Internet]. Wellington (NZ): Ministry of Health; 2018. Available from: https://www.health.govt.nz/our-work/preventative-health-wellness/tobacco-control/smokefree-environments-legislation

10. Ministry of Health. Physical activity [Internet]. Wellington (NZ). 2021 [cited 2022 Jun 8]. Available from: https://www.health.govt.nz/our-work/preventative-health-wellness/physical-activity

11. Mackay S, Gerritsen S, Sing F, Vandevijvere S, Swinburn B. Implementing healthy food environment policies in New Zealand: nine years of inaction. Health Res. Policy Syst. [Internet]. 2022;20(1):8. Available from: https://doi.org/10.1186/s12961-021-00809-8

12. Ministry of Health. Cardiovascular disease risk assessment and management for primary care. [Internet]. 2018 [cited 2021 Jul 27]. Available from: https://www.health.govt.nz/system/files/documents/publications/cvd-risk-assessment-and-management-for-primary-care-v2.pdf

13. Ministry of Health. Wellington (NZ): Cardiovascular disease; 2018 [cited 2022 Feb 21]. Available from: https://www.health.govt.nz/our-work/populations/Māori-health/tatau-kahukura-Māori-health-statistics/nga-mana-hauora-tutohu-health-status-indicators/cardiovascular-disease

14. Atherton JJ, Sindone A, De Pasquale CG, Driscoll A, MacDonald PS, Hopper I, et al. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Guidelines for the Prevention, Detection, and Management of Heart Failure in Australia 2018. Heart, Lung Circ. 2018 Oct;27(10):1123–208.

15. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure. J Am Coll Cardiol. 2013;62(16):e147–239.

16. Ziaeian B, Fonarow GC. Epidemiology and aetiology of heart failure. Nat Rev Cardiol. 2016;13(6):368–78.

17. Schwinger RHG. Pathophysiology of heart failure. Cardiovasc Diagn Ther. 2021;11(1):263–76.

18. Steenbergen C, Frangogiannis NG. Chapter 36-Ischemic Heart Disease. In: Hill JA, Olson EN, editors. Muscle [Internet]. Academic Press; 2012 [cited 2022 Jul 26]. p. 495–521. Available from: http://www.sciencedirect.com/science/article/pii/B9780123815101000363.

19. Velagaleti R, Vasan RS. Heart Failure in the 21st Century: Is it a Coronary Artery Disease Problem or Hypertension Problem? Cardiol Clin. 2007;25(4):487–v.

20. Oh GC, Cho HJ. Blood pressure and heart failure. J. Clin. Hypertens. 2020 ;26(1):1.

21. Cahill TJ, Ashrafian H, Watkins H. Genetic Cardiomyopathies Causing Heart Failure. Circ. Res. 2013;113(6):660–75.

22. Kotecha D, Piccini JP. Atrial fibrillation in heart failure: what should we do? Eur. 2015;36(46):3250–7.

23. Lip GYH, Gibbs CR, Beevers DG. Aetiology. BMJ. 2000;320(7227):104–7.

24. Khatibzadeh S, Farzadfar F, Oliver J, Ezzati M, Moran A. Worldwide risk factors for heart failure: A systematic review and pooled analysis. International Journal of Cardiology. 2013;168(2):1186–94.

25. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, et al. 2009 Focused Update Incorporated Into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults. Circ. J. 2009;119(14):e391–479.

26. Bozkurt B, Hershberger RE, Butler J, Grady KL, Heidenreich PA, Isler ML, et al. 2021 ACC/AHA Key Data Elements and Definitions for Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Clinical Data Standards for Heart Failure). Circ Cardiovascular Qual Outcomes. 2021;14(4):e000102.

27. Dunlay SM, Givertz MM, Aguilar D, Allen LA, Chan M, Desai AS, et al. Type 2 Diabetes Mellitus and Heart Failure: A Scientific Statement From the American Heart Association and the Heart Failure Society of America. Circ. 2019;140(7):e294–324.

28. Ebong IA, Goff DC, Rodriguez CJ, Chen H, Bertoni AG. Mechanisms of Heart Failure in Obesity. Obes Res Clin Pract. 2014;8(6):e540–8.

29. Gradman AH, Alfayoumi F. From Left Ventricular Hypertrophy to Congestive Heart Failure: Management of Hypertensive Heart Disease. Prog Cardiovasc Dis. 2006;48(5):326–41.

30. Maganti K, Rigolin VH, Sarano ME, Bonow RO. Valvular Heart Disease: Diagnosis and Management. Mayo Clin Proc. 2010;85(5):483–500.

31. Cardiovascular diseases (CVDs) [Internet]. Geneva: World Health Organization; 2021 [cited 2022 Feb 1]. Available from: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)

32. Libby P, Buring JE, Badimon L, Hansson GK, Deanfield J, Bittencourt MS, et al. Atherosclerosis. Nat Rev Dis Primers. 2019;5(1):1–18.

33. Fruchart JC, Nierman MC, Stroes ESG, Kastelein JJP, Duriez P. New Risk Factors for Atherosclerosis and Patient Risk Assessment. Circ [Internet]. 2004 [cited 2022 Feb 29]; 109[suppl III]:III-15–III-19, Available from: http://www.ahajournals.org/doi/abs/10.1161/01.cir.0000131513.33892.5b

34. Rafieian-Kopaei M, Setorki M, Doudi M, Baradaran A, Nasri H. Atherosclerosis: Process, Indicators, Risk Factors and New Hopes. Int J Prev Med. 2014;5(8):927–46.

35. James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 2018;392(10159):1789–858.

36. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, et al. Heart Disease and Stroke Statistics—2018 Update: A Report From the American Heart Association. Circ. 2018;137(12):e67–492.

37. Heidenreich PA, Trogdon JG, Khavjou OA, Butler J, Dracup K, Ezekowitz MD, et al. Forecasting the Future of Cardiovascular Disease in the United States. Circ. 2011;123(8):933–44.

38. Störk S, Handrock R, Jacob J, Walker J, Calado F, Lahoz R, et al. Epidemiology of heart failure in Germany: a retrospective database study. Clin Res Cardiol. 2017;106(11):913–22.

39. Smeets M, Vaes B, Mamouris P, Akker MVD, Pottelbergh GV, Goderis G, et al. Burden of heart failure in Flemish general practices: a registry-based study in the Intego database. BMJ Open. 2019;9(1):e022972.

40. Conrad N, Judge A, Tran J, Mohseni H, Hedgecott D, Crespillo AP, et al. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. The Lancet. 2018;391(10120):572–80.

41. Sahle BW, Owen AJ, Mutowo MP, Krum H, Reid CM. Prevalence of heart failure in Australia: a systematic review. BMC Cardiovasc Disord. 2016;16(1):32.

42. Groenewegen A, Rutten FH, Mosterd A, Hoes AW. Epidemiology of heart failure. Eur J Heart Fail. 2020;22(8):1342–56.

43. van Riet EES, Hoes AW, Wagenaar KP, Limburg A, Landman MAJ, Rutten FH. Epidemiology of heart failure: the prevalence of heart failure and ventricular dysfunction in older adults over time. A systematic review. Eur J Heart Fail. 2016;18(3):242–52.

44. Gerber Y, Weston SA, Redfield MM, Chamberlain AM, Manemann SM, Jiang R, et al. A Contemporary Appraisal of the Heart Failure Epidemic in Olmsted County, Minnesota, 2000-2010. JAMA Intern Med. 2015;175(6):996–1004.

45. Christiansen MN, Køber L, Weeke P, Vasan RS, Jeppesen JL, Smith JG, et al. Age-Specific Trends in Incidence, Mortality, and Comorbidities of Heart Failure in Denmark, 1995 to 2012. Circ. 2017;135(13):1214–23.

46. Roger VL. Epidemiology of Heart Failure. Circ Res. 2013;113(6):646–59.

47. Sulo G, Igland J, Øverland S, Egeland GM, Roth GA, Vollset SE, et al. Heart failure in Norway, 2000–2014: analysing incident, total and readmission rates using data from the Cardiovascular Disease in Norway (CVDNOR) Project. Eur J Heart Fail. 2020;22(2):241–8.

48. Dorr M, Riemer U, Christ M, Stoerk S, Wachter R, TRENDS HF Germany. Hospitalizations due to heart failure: major differences between East and West Germany even 30 years after reunification. Eur. 2020;41(Supplement_2):ehaa946.0954.

49. Agbor VN, Ntusi NAB, Noubiap JJ. An overview of heart failure in low- and middle-income countries. Cardiovasc Diagn Ther. 2020;10(2):244–51.

50. Bibbins-Domingo K, Pletcher MJ, Lin F, Vittinghoff E, Gardin JM, Arynchyn A, et al. Racial Differences in Incident Heart Failure among Young Adults. NEJM. 2009 ;360(12):1179–90.

51. Bragazzi NL, Zhong W, Shu J, Abu Much A, Lotan D, Grupper A, et al. Burden of heart failure and underlying causes in 195 countries and territories from 1990 to 2017. EJPC. 2021;28(15):1682–90.

52. Ministry of Health. New Zealand Health Survey [Internet]. Wellington (NZ): Annual Data Explorer; 2021 [cited 2022 Aug 3]. Available from:

https://minhealthnz.shinyapps.io/nz-health-survey-2020-21-annual-data-explorer/_w_0a4bb45d/#!/explore-indicators

53. Wells S, Riddell T, Kerr A, Pylypchuk R, Chelimo C, Marshall R, et al. Cohort Profile: The PREDICT Cardiovascular Disease Cohort in New Zealand Primary Care (PREDICT-CVD 19). Int J Epidemiol. 2017;46(1):22–22.

54. Selak V, Poppe K, Grey C, Mehta S, Winter-Smith J, Jackson R, et al. Ethnic differences in cardiovascular risk profiles among 475,241 adults in primary care in Aotearoa, New Zealand. N Z Med J. 2020;133(1521):14-5.

55. Wasywich CA, Gamble GD, Whalley GA, Doughty RN. Understanding changing patterns of survival and hospitalization for heart failure over two decades in New Zealand: utility of 'days alive and out of hospital' from epidemiological data. Eur J Heart Fail. 2010;12(5):462–8.

56. Labrosciano C, Horton D, Air T, Tavella R, Beltrame JF, Zeitz CJ, et al. Frequency, trends and institutional variation in 30-day all-cause mortality and unplanned readmissions following hospitalisation for heart failure in Australia and New Zealand. Eur J Heart Fail. 2021;23(1):31–40.

57. Riddell T. Heart failure hospitalisations and deaths in New Zealand: patterns by deprivation and ethnicity. N Z Med J. 2005;118(1208):U1254.

58. Somaratne P. Secondary and Tertiary Prevention at Different Stages in the Development of Heart Failure [PHD]. Auckland (NZ): University of Auckland; 2009 [cited 2022 Feb 21]. Available from: https://researchspace.auckland.ac.nz/handle/2292/22160

59. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. Eur. 2021;42(36):3599–726.

60. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circ. 2022;145(18):e895–1032.

61. Joshi SS, Singh T, Newby DE, Singh J. Sodium-glucose co-transporter 2 inhibitor therapy: mechanisms of action in heart failure. Heart. 2021;107(13):1032–8.

62. Goldenberg I, Kutyifa V, Klein HU, Cannom DS, Brown MW, Dan A, et al. Survival with Cardiac-Resynchronization Therapy in Mild Heart Failure. NEJM. 2014; 370(18):1694–701.

63. Tang ASL, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, et al. Cardiac-Resynchronization Therapy for Mild-to-Moderate Heart Failure. NEJM. 2010;363(25):2385–95.

64. Dalén M, Lund LH, Ivert T, Holzmann MJ, Sartipy U. Survival After Coronary Artery Bypass Grafting in Patients With Preoperative Heart Failure and Preserved vs Reduced Ejection Fraction. JAMA Cardiol. 2016; 1(5):530–8.

65. Pylypchuk R, Wells S, Kerr A, Poppe K, Riddell T, Harwood M, et al. Cardiovascular disease risk prediction equations in 400 000 primary care patients in New Zealand: a derivation and validation study. The Lancet. 2018 May 12;391(10133):1897–907.

66. Tran NK, Lash TL, Goldstein ND. Practical data considerations for the modern epidemiology student. Global Epidemiology. 2021;3:100066.

67. Higgins JPT. Commentary: Heterogeneity in meta-analysis should be expected and appropriately quantified. Int J Epidemiol. 2008;37(5):1158–60.

68. Kornegay C, Segal JB. Selection of Data Sources [Internet]. Developing a Protocol for Observational Comparative Effectiveness Research: A User's Guide. AHRQ; 2013 [cited 2022 Mar 26]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK126195/

69. Stanfill MH, Williams M, Fenton SH, Jenders RA, Hersh WR. A systematic literature review of automated clinical coding and classification systems. J Am Med Inform Assoc. 2010;17(6):646–51.

70. World Health Organization. International Classification of Diseases (ICD) [Internet]. Geneva: World Health Organization; 2022 [cited 2022 Mar 15]. Available from: https://www.who.int/standards/classifications/classification-of-diseases

71. Brämer GR. International statistical classification of diseases and related health problems. Tenth revision. World Health Stat Q. 1988;41(1):32–6.

72. Centers for Medicare and Medicaid Services. ICD-10-CM Official Guidelines for Coding and Reporting FY 2020 [Internet]. Atlanta (US): The Centers for Disease Control and Prevention; 2020 [cited 2022 Aug 17]. Available from: https://hhsgovfedramp.gov1.qualtrics.com/jfe/form/SV_3Jyxvg4zv8sPGrH?Q_CHL=si&Q_CanScreenCapture=1

73. Hirsch JA, Nicola G, McGinty G, Liu RW, Barr RM, Chittle MD, et al. ICD-10: History and Context. AJNR Am J Neuroradiol. 2016 Apr;37(4):596–9.

74. McCormick N, Lacaille D, Bhole V, Avina-Zubieta JA. Validity of Heart Failure Diagnoses in Administrative Databases: A Systematic Review and Meta-Analysis. PLoS One. 2014 Aug 15;9(8):e104519.

75. NHS Digital. Read Codes [Internet]. England: NHS Digital; 2020 [cited 2022 Aug 15]. Available from: https://digital.nhs.uk/services/terminology-and-classifications/read-codes

76. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. Ann Intern Med. 2018 Oct 2;169(7):467–73.

77. Canova C, Cantarutti A. Population-Based Birth Cohort Studies in Epidemiology. Int J Environ Res Public Health. 2020 Aug;17(15):5276.

78. Khan SS, Ning H, Sinha A, Wilkins J, Allen NB, Vu THT, et al. Cigarette Smoking and Competing Risks for Fatal and Nonfatal Cardiovascular Disease Subtypes Across the Life Course. JAHA. 2021 Dec 7;10(23):e021751.

79. Khan SS, Ning H, Allen NB, Carnethon MR, Yancy CW, Shah SJ, et al. Development and Validation of a Long-Term Incident Heart Failure Risk Model. Circ. 2022 Jan 21;130(2):200–9.

80. Bavishi A, Bruce M, Ning H, Freaney PM, Glynn P, Ahmad FS, et al. Predictive Accuracy of Heart Failure-Specific Risk Equations in an Electronic Health Record-Based Cohort. Circ Heart Fail. 2020 Nov;13(11):e007462.

81. Rethy LB, McCabe ME, Kershaw KN, Ahmad FS, Lagu T, Pool LR, et al. Neighborhood Poverty and Incident Heart Failure: An Analysis of Electronic Health Records from 2005 to 2018. J GEN INTERN MED. 2021 Dec 1;36(12):3719–27.

82. Ambale-Venkatesh B, Yoneyama K, Sharma RK, Ohyama Y, Wu CO, Burke GL, et al. Left ventricular shape predicts different types of cardiovascular events in the general population. Heart. 2017 Apr 1;103(7):499–507.

83. Charry D, Xu J, Tanaka H, Heffernan KS, Richardson MR, Churilla JR. Total brachial artery reactivity and incident heart failure and heart failure subtypes: multi-ethnic study of atherosclerosis. Heart Vessels. 2022 Mar 1;37(3):411–8.

84. Steffen BT, Duprez D, Bertoni AG, Guan W, Tsai MY. Lipoprotein(a)-related risk of heart failure is evident in Caucasians but not in other racial/ethnic groups: The Multi-Ethnic Study of Atherosclerosis. Arterioscler Thromb Vasc Biol. 2018 Oct;38(10):2498–504.

85. de Lemos JA, Ayers CR, Levine B, deFilippi CR, Wang TJ, Hundley WG, et al. A Multimodality Strategy for Cardiovascular Risk Assessment: Performance in Two Population-Based Cohorts. Circ. 2017 May 30;135(22):2119–32.

86. Cooper LL, Rong J, Pahlevan NM, Rinderknecht DG, Benjamin EJ, Hamburg NM, et al. Intrinsic Frequencies of Carotid Pressure Waveforms Predict Heart Failure Events. J. Hypertens. 2021 Feb;77(2):338–46.

87. Nwabuo CC, Moreira HT, Vasconcellos HD, Mewton N, Opdahl A, Ogunyankin KO, et al. Left ventricular global function index predicts incident heart failure and cardiovascular disease in young adults: the coronary artery risk development in young adults (CARDIA) study. Eur Heart J Cardiovasc Imaging. 2019 May;20(5):533–40.

88. Ndumele CE, Matsushita K, Lazo M, Bello N, Blumenthal RS, Gerstenblith G, et al. Obesity and Subtypes of Incident Cardiovascular Disease. J Am Heart Assoc. 2016 Jul 28;5(8):e003921.

89. Garfield LD, Scherrer JF, Hauptman PJ, Freedland KE, Chrusciel T, Balasubramanian S, et al. Association of anxiety disorders and depression with incident heart failure. Psychosom Med. 2014 Feb;76(2):128–36.

90. White JR, Chang CCH, So-Armah KA, Stewart JC, Gupta SK, Butt AA, et al. Depression and HIV Infection are Risk Factors for Incident Heart Failure Among Veterans: Veterans Aging Cohort Study. Circ. 2015 Oct 27;132(17):1630–8.

91. George J, Rapsomaniki E, Pujades-Rodriguez M, Shah AD, Denaxas S, Herrett E, et al. How Does Cardiovascular Disease First Present in Women and Men? Circ. 2015 Oct 6;132(14):1320–8.

92. Shah AD, Langenberg C, Rapsomaniki E, Denaxas S, Pujades-Rodriguez M, Gale CP, et al. Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1·9 million people. Lancet Diabetes Endocrinol. 2015 Feb;3(2):105–13.

93. Rautiainen S, Levitan EB, Mittleman MA, Wolk A. Fruit and vegetable intake and rate of heart failure: a population-based prospective cohort of women. Eur J Heart Fail. 2015;17(1):20–6.

94. Welsh C e., Welsh P, Jhund P, Delles C, Celis-Morales C, Lewsey J d., et al. Urinary Sodium Excretion, Blood Pressure, and Risk of Future Cardiovascular Disease and Mortality in Subjects Without Prior Cardiovascular Disease. J Hypertens. 2019 Jun;73(6):1202–9.

95. Leening MJG, Ferket BS, Steyerberg EW, Kavousi M, Deckers JW, Nieboer D, et al. Sex differences in lifetime risk and first manifestation of cardiovascular disease: prospective population based cohort study. BMJ. 2014 Nov 17;349:g5992.

96. Fukui A, Kaneko H, Okada A, Yano Y, Itoh H, Matsuoka S, et al. Semiquantitative assessed proteinuria and risk of heart failure: analysis of a nationwide epidemiological database. Nephrol. Dial. Transplant.. 2021 Sep 7;gfab248.

97. Matsuoka S, Kaneko H, Okada A, Itoh H, Suzuki Y, Fujiu K, et al. Association of retinal atherosclerosis assessed using Keith-Wagener-Barker system with incident heart failure and other atherosclerotic cardiovascular disease: Analysis of 319,501 individuals from the general population. Atherosclerosis [Internet]. 2022 Feb 26 [cited 2022 Apr 1]; Available from: https://www.sciencedirect.com/science/article/pii/S0021915022001071

98. Kim OJ, Lee SH, Kang SH, Kim SY. Incident cardiovascular disease and particulate matter air pollution in South Korea using a population-based and nationwide cohort of 0.2 million adults. J. Environ.Health. 2020 Nov 9;19(1):113.

99. Ferraro RA, Ogunmoroti O, Zhao D, Ndumele CE, Rao V, Pandey A, et al. Hepatocyte Growth Factor and Incident Heart Failure Subtypes: The Multi-Ethnic Study of Atherosclerosis (MESA). J Card Fail. 2021 Sep 1;27(9):981–90.

100. Nagai K, Tanaka T, Kodaira N, Kimura S, Takahashi Y, Nakayama T. Data resource profile: JMDC claims database sourced from health insurance societies. J. Gen. Fam. Med. 2021;22(3):118–27.

101. Wilkins JT, Karmali KN, Huffman MD, Allen NB, Ning H, Berry JD, et al. Data Resource Profile: The Cardiovascular Disease Lifetime Risk Pooling Project. Int J Epidemiol. 2015 Oct 1;44(5):1557–64.

102. Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol. 2015 Jun 1;44(3):827–36.

103. Rothman KJ, Greenland S. Validity and Generalizability in Epidemiologic Studies. In: Armitage P, Colton T, editors. Encyclopedia of Biostatistics [Internet]. 2nd ed. US: John Wiley & Sons, Ltd; 2005 [cited 2022 Apr 16]. Available from: http://onlinelibrary.wiley.com/doi/abs/10.1002/0470011815.b2a03129

104. Ellenberg JH. Selection bias in observational and experimental studies. Stat Med. 1994;13(5–7):557–67.

105. Ellenberg JH, Nelson KB. Sample Selection and the Natural History of Disease: Studies of Febrile Seizures. JAMA. 1980 Apr 4;243(13):1337–40.

106. Saczynski JS, Andrade SE, Harrold LR, Tjia J, Cutrona SL, Dodd KS, et al. A systematic review of validated methods for identifying heart failure using administrative data. Pharmacoepidemiol Drug Saf. 2012 Jan 19;21:129–40.

107. Bottle A, Kim D, Aylin P, Cowie MR, Majeed A, Hayhoe B. Routes to diagnosis of heart failure: observational study using linked data in England. Heart. 2018 Apr 1;104(7):600–5.

108. Denaxas S, Gonzalez-Izquierdo A, Direk K, Fitzpatrick NK, Fatemifar G, Banerjee A, et al. UK phenomics platform for developing and validating electronic health record phenotypes: CALIBER. J Am Med Inform Assoc. 2019 Jul 22;26(12):1545–59.

109. Hancock HC, Close H, Fuat A, Murphy JJ, Hungin APS, Mason JM. Barriers to accurate diagnosis and effective management of heart failure have not changed in the past 10 years: a qualitative study and national survey. BMJ Open. 2014 Mar 1;4(3):e003866.

110. Taylor CJ. Diagnosing heart failure: challenges in primary care. Heart. 2019 May 1;105(9):663–4.

111. Ferreira JP, Metra M, Mordi I, Gregson J, ter Maaten JM, Tromp J, et al. Heart failure in the outpatient versus inpatient setting: findings from the BIOSTAT-CHF study. Eur J Heart Fail. 2019;21(1):112–20.

112. Faridi KF, Tamez H, Butala NM, Song Y, Shen C, Secemsky EA, et al. Comparability of Event Adjudication Versus Administrative Billing Claims for Outcome Ascertainment in the DAPT Study. Circ Cardiovas Qual Outcomes. 2021 Jan;14(1):e006589.

113. Lakshminarayan K, Larson JC, Virnig B, Fuller C, Allen NB, Limacher M, et al. Comparison of Medicare Claims vs. Physician Adjudication for Identifying Stroke Outcomes in the Women's Health Initiative. Stroke. 2014 Mar;45(3):815–21.

114. Fort D, Weng C, Bakken S, Wilcox AB. Considerations for Using Research Data to Verify Clinical Data Accuracy. AMIA Jt Summits Transl Sci Proc. 2014 Apr 7;2014:211–7.

115. Newell SA, Girgis A, Sanson-Fisher RW, Savolainen NJ. The accuracy of self-reported health behaviors and risk factors relating to cancer and cardiovascular disease in the general population 1: A critical review. Am J Prev Med. 1999 Oct 1;17(3):211–29.

116. Short ME, Goetzel RZ, Pei X, Tabrizi MJ, Ozminkowski RJ, Gibson TB, et al. How Accurate are Self-Reports? An Analysis of Self-Reported Healthcare Utilization and Absence When Compared to Administrative Data. J Occup Environ Med. 2009 Jul;51(7):786–96.

117. Delgado-Rodríguez M, Llorca J. Bias. J Epidemiology Community Health. 2004 Aug 1;58(8):635–41.

118. Althubaiti A. Information bias in health research: definition, pitfalls, and adjustment methods. J Multidiscip Healthc. 2016 May 4;9:211–7.

119. Burgard SA, Chen PV. Challenge of Health Measurement in Studies of Health Disparties. Soc Sci Med. 2014 Apr;106:143–50.

120. Dey AK, Alyass A, Muir RT, Black SE, Swartz RH, Murray BJ, et al. Validity of Self-Report of Cardiovascular Risk Factors in a Population at High Risk for Stroke. J Stroke Cerebrovasc Dis. 2015 Dec 1;24(12):2860–5.

121. Cadarette SM, Wong L. An Introduction to Health Care Administrative Data. Can J Hosp Pharm. 2015;68(3):232–7.

122. Ahmad FS, Chan C, Rosenman MB, Post WS, Fort DG, Greenland P, et al. Validity of Cardiovascular Data From Electronic Sources. Circ [Internet]. 2017 Sep [cited 2022 May 13]; Available from: http://www.ahajournals.org/doi/abs/10.1161/CIRCULATIONAHA.117.027436

123. Arana A, Margulis AV, Varas-Lorenzo C, Bui CL, Gilsenan A, McQuay LJ, et al. Validation of cardiovascular outcomes and risk factors in the Clinical Practice Research Datalink in the United Kingdom. Pharmacoepidemiol Drug Saf. 2021 Feb;30(2):237–47.

124. Selak V, Kerr A, Poppe K, Wu B, Harwood M, Grey C, et al. Annual Risk of Major Bleeding Among Persons Without Cardiovascular Disease Not Receiving Antiplatelet Therapy. JAMA. 2018 Jun 26;319(24):2507–20.

125. University of Auckland. PREDICT (Enigma) / VIEW (University of Auckland), looking forward to 2016. | Enigma Solutions Ltd [Internet]. Auckland (NZ): University of Auckland; 2015 [cited 2022 Feb 2]. Available from: https://www.enigma.co.nz/2015/12/23/predict-enigma-view-university-of-auckland-looking-forward-to-2016/

126. University of Auckland. Wiki [Internet]. Auckland (NZ): Univeristy of Auckland; 2022 [cited 2022 Feb 2]. Available from: https://wiki.auckland.ac.nz/pages/viewpage.action?pageId=153562344

127. Mehta S, Jackson R, Pylypchuk R, Poppe K, Wells S, Kerr AJ. Development and validation of alternative cardiovascular risk prediction equations for population health

planning: a routine health data linkage study of 1.7 million New Zealanders. Int J Epidemiol. 2018 Oct 1;47(5):1571–84.

128. Sanchis-Gomar F, Perez-Quilis C, Leischik R, Lucia A. Epidemiology of coronary heart disease and acute coronary syndrome. Ann Transl Med. 2016 Jul;4(13):256.

129. Hein AM, Scialla JJ, Sun JL, Greene SJ, Shaw LK, Chiswell K, et al. Estimated Glomerular Filtration Rate Variability in Patients With Heart Failure and Chronic Kidney Disease. J Card Fail. 2021 Nov 1;27(11):1175–84.

130. Lam CSP, Arnott C, Beale AL, Chandramouli C, Hilfiker-Kleiner D, Kaye DM, et al. Sex differences in heart failure. Eur Heart J. 2019 Dec 14;40(47):3859–3868c.

131. StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP. Available from: https://www.stata.com/support/faqs/resources/citing-software-documentation-faqs/

132. Miller VM. Universality of sex differences in cardiovascular outcomes: where do we go from here? Eur Heart J. 2020 May 1;41(17):1697–9.

133. Feldman RD. Sex-Specific Determinants of Coronary Artery Disease and Atherosclerotic Risk Factors: Estrogen and Beyond. Can J Cardiol. 2020 May 1;36(5):706–11.

134. Dayan N, Udell JA. Moving Toward Sex-Specific Cardiovascular Risk Estimation. Can J Cardiol. 2020 Jan 1;36(1):13–5.

135. Elgendy IY, Mahtta D, Pepine CJ. Medical Therapy for Heart Failure Caused by Ischemic Heart Disease. Circ. 2019 May 24;124(11):1520–35.

136. Severino P, D'Amato A, Pucci M, Infusino F, Birtolo LI, Mariani MV, et al. Ischemic Heart Disease and Heart Failure: Role of Coronary Ion Channels. Int J Mol Sci. 2020 Apr 30;21(9):3167.

137. Andersson C, Weeke P, Pecini R, Kjaergaard J, Hassager C, Køber L, et al. Long-term impact of diabetes in patients hospitalized with ischemic and non-ischemic heart failure. Scand Cardiovasc J. 2010 Jan 1;44(1):37–44.

138. Kaltoft M, Langsted A, Nordestgaard BG. Obesity as a Causal Risk Factor for Aortic Valve Stenosis. J Am Coll Cardiol. 2020 Jan 21;75(2):163–76.

139. George J, Mathur R, Shah AD, Pujades-Rodriguez M, Denaxas S, Smeeth L, et al. Ethnicity and the first diagnosis of a wide range of cardiovascular diseases: Associations in a linked electronic health record cohort of 1 million patients. PLOS ONE. 2017 Jun 9;12(6):e0178945.

140. Denaxas SC, George J, Herrett E, Shah AD, Kalra D, Hingorani AD, et al. Data Resource Profile: Cardiovascular disease research using linked bespoke studies and electronic health records (CALIBER). Int J Epidemiol. 2012 Dec 1;41(6):1625–38.

141. Raleigh V, Holmes J. The health of people from ethnic minority groups in England [Internet]. The King's Fund. 2021 [cited 2022 Aug 20]. Available from: https://www.kingsfund.org.uk/publications/health-people-ethnic-minority-groups-england

142. Ministry of Health. Tatau Kahukura: Māori Health Chart Book 2015, 3rd edition [Internet]. Ministry of Health NZ. 2015 [cited 2022 Jul 2]. Available from:

143. Ministry of Health. Tupu Ola Moui: Pacific Health Chart Book 2012 [Internet]. Wellington (NZ): Ministry of Health NZ; 2012 [cited 2022 Jul 2]. Available from: https://www.health.govt.nz/publication/tupu-ola-moui-pacific-health-chart-book-2012

144. Statistics New Zealand. 2018 Census population and dwelling counts [Internet]. Auckland (NZ): Statistics New Zealand; 2018 [cited 2022 Jul 3]. Available from: https://www.stats.govt.nz/information-releases/2018-census-population-and-dwelling-counts

145. Ministry of Health. Tagata Pasifika in New Zealand [Internet]. Wellington (NZ): Ministry of Health; 2017 [cited 2022 Jul 3]. Available from: https://www.health.govt.nz/our-work/populations/pacific-health/tagata-pasifika-new-zealand

146. Pujades-Rodriguez M, Timmis A, Stogiannis D, Rapsomaniki E, Denaxas S, Shah A, et al. Socioeconomic Deprivation and the Incidence of 12 Cardiovascular Diseases in 1.9 Million Women and Men: Implications for Risk Prediction and Prevention. PLOS ONE. 2014 Aug 21;9(8):e104671.

147. Crampton P, Salmond C, Atkinson J. A comparison of the NZDep and New Zealand IMD indexes of socioeconomic deprivation. Kōtuitui: New Zealand Journal of Social Sciences Online. 2020 Jan 2;15(1):154–69.

148. Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing data in randomised clinical trials – a practical guide with flowcharts. BMC Med Res Methodol. 2017 Dec 6;17(1):162.

149. Ministry of Health. Obesity [Internet]. Wellington (NZ): Ministry of Health; 2022 [cited 2022 Aug 20]. Available from: https://www.health.govt.nz/our-work/diseases-and-conditions/obesity

150. Sport New Zealand. Healthy Active Learning - Ihi Aotearoa [Internet]. Wellington (NZ): Sport New Zealand | Ihi Aoteroa; 2022 [cited 2022 Aug 20]. Available from: https://sportnz.org.nz/get-active/ways-to-get-active/physical-education/healthy-active-learning/

151. Ministry of Health. Clinical Guidelines for Weight Management in New Zealand Children and Young People [Internet]. Wellington (NZ): Ministry of Health. 2016 [cited 2022 May 21]. Available from: https://www.health.govt.nz/publication/clinical-guidelines-weight-management-new-zealand-children-and-young-people

152. Ministry for Primary Industries. How do trans-fatty acids affect your health? | MPI - Ministry for Primary Industries. A New Zealand Government Department. [Internet]. Wellington (NZ): Ministry for Primary Industries; 2022 [cited 2022 May 21]. Available

from: https://www.mpi.govt.nz/food-safety-home/safe-eat/how-do-trans-fatty-acids-affect-your-health/

153. Ministry of Health NZ. Te Tiriti o Waitangi [Internet]. Wellington (NZ): Ministry of Health; 2020 [cited 2022 May 21]. Available from: https://www.health.govt.nz/our-work/populations/Māori-health/te-tiriti-o-waitangi

154. Ministry of Health. Whakamaua: Māori Health Action Plan 2020-2025 [Internet]. Wellington (NZ): Ministry of Health NZ; 2021 [cited 2022 May 21]. Available from: https://www.health.govt.nz/publication/whakamaua-Māori-health-action-plan-2020-2025

155. Ministry of Health. Pae Ora (Healthy Futures) Act [Internet]. Wellington (NZ): Ministry of Health NZ; 2022 [cited 2022 May 21]. Available from: https://www.health.govt.nz/about-ministry/what-we-do/pae-ora-healthy-futures-act

156. Ministry of Health. Strategic frameworks [Internet]. Wellington (NZ): Ministry of Health NZ. 2021 [cited 2022 May 21]. Available from: https://www.health.govt.nz/our-work/populations/pacific-health/strategic-frameworks

157. World Health Organization. Social determinants of health [Internet]. Geneva: World Health Organization. 2022 [cited 2022 May 21]. Available from: https://www.who.int/health-topics/social-determinants-of-health

158. McMaughan DJ, Oloruntoba O, Smith ML. Socioeconomic Status and Access to Healthcare: Interrelated Drivers for Healthy Aging. Front Public Health. 2020 Jun 18;8:231.

159. Health Quality and Safety Commission. Updated data shows cost the main barrier to accessing health services [Internet]. Wellington (NZ): Health Quality and Safety Commission; 2020 [cited 2022 Aug 01]. Available from: https://www.hqsc.govt.nz/news/updated-data-shows-cost-the-main-barrier-to-accessing-health-services/

160. Ministry of Health. HISO 10001:2017 ethnicity data protocols. Wellington, New Zealand: Ministry of Health; 2017.

161. Ministry of Health. Neighbourhood deprivation [Internet]. Wellington (NZ): Ministry of Health NZ; 2018 [cited 2022 Aug 01]. Available from: https://www.health.govt.nz/our-work/populations/Māori-health/tatau-kahukura-Māori-health-statistics/nga-awe-o-te-hauora-socioeconomic-determinants-health/neighbourhood-deprivation

162. World Health Organization. Obesity and overweight [Internet]. Geneva (Switzerland): World Health Organization; 2022 [cited 2022 Aug 17]. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight

Appendices

Appendix 1: The source, types and definition of variables

Variables	Types	Source	Methods of measurement
Sex	Binary	PREDICT NHI database	Sex documented on NHI database
Age in years	Continuous	PREDICT NHI database	Age at index PREDICT assessment
Self-identified ethnicity	Categorical	PREDICT NHI database	Ethnicities include New Zealand Māori, Pacific, Indian, Chinese/other Asian, European. The priorities output method based on national ethnicity data protocols is used when participants self-identify with more than one of the listed ethnicities(160). The known elevated risk of CVD according to ethnicity is NZ Māori > Pacific > South Asian > Chinese and other East Asian > European > MELAA > Other > Unknown/not answered/not identifiable (No_not_stated). Due to small numbers, participants self-identify with the last three ethnicities (MELAA [Middle Eastern/Latin American/African], Other and Unkown) were not included in the analysis.
New Zealand Index of Socioeconomic Deprivation	Continuous	NHI database	NZDep is an area-based socio-economic deprivation score constructed from 9 census derived variables(161). In this study, deprivation quintiles (1=least deprived, 5=most deprived) were used, i.e. Deprivation quintile 1 (least deprived) = NZ Dep decile 1 or 2 Deprivation quintile 2 = NZ Dep decile 3 or 4 Deprivation quintile 3 = NZ Dep decile 5 or 6 Deprivation quintile 4 = NZ Dep decile 7 or 8 Deprivation quintile 5 (most deprived) = NZ Dep decile 9 or 10
Family history of premature CVD	Binary	PREDICT	Participants' first-degree male relative was diagnosed with CVD before 55 years old, or a first-degree female relative was diagnosed with CVD before 65 years old.
Smoking status	Categorical	PREDICT	Never smoker = never smoker at index assessment Ex-smoker = quit over 12 months ago; quit less than 12 months ago Current smoker = smokes up to 10 cigarettes/day, 11-19 cigs/day or 20+ cigs/day at index assessment
Diabetes	Binary	Multiple	Participants were classified as having diabetes if they had history of diabetes (PREDICT) AND/OR prior hospitalization with diabetes or relevant condition noted (ICD-10-AM E10-14) AND/OR took diabetes medications prior to the index assessment (see Appendices 2 for medication included in class)
BMI	Categorical	PREDICT	BMI obtained at index assessment and categorized into underweight with BMI cut-off points <18.5, normal weight with BMI cut-off points 18.5 to <25, overweight with BMI cut-off points 25.0 to <30 and obesity with BMI cut-off points 30.0 or higher according to WHO's definition (162)

History of atrial fibrillation	Binary	PREDICT	Participants were classified as having atrial fibrillation if they had prior hospitalization due to atrial fibrillation (ICD-10-AM I480-I484/I489.
Systolic blood pressure (SBP)	Continuous	PREDICT	Mean of the two systolic BP measurement recorded at the time of the index assessment.
Diastolic blood pressure (DBP)	Continuous	PREDICT	Mean of the two diastolic BP measurement recorded at the time of the index assessment.
Total cholesterol to High Density Lipoprotein cholesterol (TC/HDL) ratio	Continuous	PREDICT TestSafe	The TC and HDL level measured in community laboratories and downloaded into patient records. The laboratory measures recorded most recently at the time of the index assessment are used.
Blood pressure lowering medication	Binary	Pharms	At least one medication dispensed during the six months prior to the index PREDICT risk assessment (see Appendices 2 for medication included in class).
Antithrombotic medication	Binary	Pharms	At least one medication dispensed during the six months prior to the index PREDICT risk assessment (see Appendices 2 for medication included in class).
Lipid lowering medication	Binary	Pharms	At least one medication dispensed during the six months prior to the index PREDICT risk assessment (see Appendices 2 for medication included in class)
History of cardiac valvular disease	Binary	NMDS	Participants were classified as having valvular disease if there were recording of any procedure (ACHI) or ICD-10 code that relates to a disorder of a native intracardiac valve or describes the presence of a prosthetic intracardiac valve (check appendix 4)
History of cardiomyopathy	Binary	NMDS	Participants were classified as having cardiomyopathy if there were recording of any ICD-10 code associated with cardiomyopathy of any etiology (check appendix 4)
History of prothesis implanted	Binary	NMDS	Participants were classified as having prothesis implanted if there were recording of any procedure related to an intracardiac pacemaker or implanted cardioverter defibrillator, and any ICD-10 code that describes a complication associated with an electronic or mechanical or vascular device or prosthesis or graft. (check appendix 4)
eGFR	Continuous	TestSafe	eGFR is calculated based on the serum creatinine in mg/dl (Scr) result which was closest to baseline, within 2 years prior and 14 days post baseline, using the CKD-Epi equation(126).
Five-year absolute risk of CVD (%) score	Continuous	PREDICT	The risk score is calculated based on PREDICT-1^0 risk score(126),

BMI=body mass index, CKD-Epi=Chronic Kidney Disease Epidemiology Collaboration, ICD=International Classification of Diseases, eGFR=estimated glomerular filtration rate, NHI=National Health Index, NMDS=National Minimum Dataset, Pharms =Pharmaceutical Information Database, WHO=World Health Organization

Appendix 2: ICD-10-codes used to determine history or outcome of CVD from hospital records.

Category	Event	ICD-10 Clinical Code	Exclude
Coronary Heart Disease	History/ Outcome	Unstable angina I200, NSTEMI I214, STEMI I210-I213/ I220-I221/ I228-I229, Angina I201/ I208-I209, Atrial fibrillation I480-I484/ I489	
	History only	MI unspecified I219, Old MI I252,	
Coronary Procedures	History/Outcome	PCI 3530400 - 3530500 / 3531000 - 3531002 / 3830000 / 3830600 - 3830602 / 3830900 / 3831200 - 3831201 / 3831500 / 3831800 - 38318 01 / 9021800 - 9021801 / Z955 / CABG 3849700 - 3849707 / 3850000 - 3850004 / 3850300 - 3850304 / 3850500 / 3863700 / 9020100 - 9020103 /Z950	Omit Z955 (represents presence of coronary angioplasty implant and graft), Z951 (represents presence of aortocoronary bypass graft)
	History	Other Coronary Procedures 3530401 / 3530501 / 3531003 - 3531005 / 3845619 / 3850500 / 3850700 / 3850800 / 3850900	
Cerebral Vascular Disease	History/ Outcome	Ischaemic stroke I630-I636/ I638-I639/ I64/ I693-I694, TIA 450 - G453 / G458 - G459, Other CeVD G460 - G468 / I660 - I664 / I668 - I670 / I672 / I698	Omit I693-I694, I698 if it is used as an outcome category (as I693-I694represent sequelae of cerebral infarction and I698 represent sequelae of other Cevd)
Haemorrhagic Stroke	History/ Outcome	I600 - I616 / I618 - I619 / I690 - I691	Omit I690 (sequelae of nontraumatic subarachnoid hemorrhage) I691(sequelae of nontraumatic intracerebral hemorrhage) if outcome
Heart Failure	History/ Outcome	I110 / I130 / I132 / I50 / I500 – I501 / I509	
Peripheral Vascular Disease	History/ Outcome	Atherosclerosis with symptoms: I702 a, Atherosclerosis (other): I700, I701, I7020, I708, I709, Aortic aneurysm and dissection: I71 a , PVD, unspecified: I739, Arterial embolism and thrombosis: I74 a, DM with peripheral circulatory complications DM with other circulatory complications: E105 a, E115 a , E145 a	Omit if outcome: I700 (atherosclerosis of aorta) , I701 (atherosclerosis of renal artery) ,I7020 (unspecified atherosclerosis of native arteries of extremities), I 708 (atherosclerosis of other arteries) ,I709 (other and unspecified atherosclerosis), I714

			(abdominal aortic aneurysm, without rupture), I716 (thoracoabdominal aortic aneurysm, without rupture), I717
Peripheral Vascular Disease Procedures		The following procedures: aneurysm excisions, repairs and replacements, bypasses, endarterectomies and patch grafts, resections and re-anastomoses Involving the following arteries: carotid: 327000-3271011, 3270300, 3310000, 3350000 aorta: 3270800-3270803, 3311200, 3311500, 3311800, 3312100, 3315100, 3315400, 3315700, 3316000, 3350900, 3351200, 3351500 femoral: 3271200-3271201, 3271500-3271503, 3271800-3271801, 3273900, 3274200, 3274500, 3274800, 3275100-3275103, 3275400-3275402, 3275700-3275701, 3351501, 3352100, 3354200 mesenteric : 3273000-3273001, 3273300-3273301, 3273600, 3353001, 3353300, 3353600 other: 3276300-3276303, 3276305-3276314, 3276316-3276319, 3305000, 3305500, 3307500, 3308000, 3312400, 3312700, 3313000, 3316300, 3317800, 3318100, 3350600-3350601, 3351800, 3352400, 3352700, 3353000, 3353900, 3354800-3354803, 3355100, 3355400, 3530306-3530307, 3531200-3531201,3531500-3531501, , 9022900, 902300	
Mortality of broad CVD	Mortality	Same as outcome of broad CVD which includes CHD, Cevd, PVD, HS and HF but excludes coronary procedures and peripheral vascular procedures.	
Mortality of other related CVD Deaths (This is death only variable and no equivalent codes can be found in hospitalisation outcomes)	Mortality	E1053 / E1059 / E1153 / E1159 / E1353 / E1359 / E1453 / E1459 / I250 / I2510 - I2513 / I252 / I258 - I259 / I690 - I691 / I693 - I694 / I698 / I700 - I701 / I7020 / I708 - I709 / I714 / I716	

CVD=cardiovascular disease, CeVD=cerebrovascular disease, CHD=coronary heart disease, CABG=coronary artery bypass graft surgery

DM=diabetes mellitus, HF=heart failure, ICD-10-AM= International Statistical Classification of Diseases and Related Health Problems, Australian Modification, HS= haemorrhagic stroke, MI=myocardial infarction, NSTEMI=non-ST-elevation myocardial infarction, PCI= percutaneous coronary intervention, PVD=peripheral vascular disease, TIA=transient (cerebral) ischaemic attack, STEMI= ST-elevation myocardial infarction

a Includes any subcategories that come after the last number, unless specified as excluded

Appendix 3: Medication included in drug classes

Blood pressure lowering medication	Antithrombotic medication	Lipid lowering medication	Treat other diseases
Captopril, Perindopril, Lisinopril, Benazepril, Quinapril, Cilazapril, Enalapril maleate, Trandolapril, Quinapril with hydrochlorothiazide, Captopril with hydrochlorothiazide, Lisinopril with hydrochlorothiazide, Enalapril maleate with hydrochlorothiazide, Cilazapril with hydrochlorothiazide Losartan with hydrochlorothiazide, Candesartan cilexetil, Losartan potassium, Losartan with Hydrochlorothiazide, Losartan potassium with hydrochlorothiazide, Losartan Carvedilol, Celiprolol, Timolol, Sotalol, Propranolol, Pindolol, Oxprenolol, Nadolol, Metoprolol tartrate, Metoprolol succinate, Labetalol, Atenolol, Alprenolol, Acebutolol, Acebutolol with hydrochlorothiazide, Pindolol with clopamide, Atenolol with chlorthalidone, Bisoprolol fumarate Amlodipine, Diltiazem hydrochloride, Felodipine, Isradipine, Nifedipine, Verapamil hydrochloride, Verapamil Hydrochloride Acebutolol with hydrochlorothiazide, Amiloride hydrochloride with hydrochlorothiazide, Atenolol with chlorthalidone, Bendrofluazide, Bendroflumethiazide [Bendrofluazide], Captopril with hydrochlorothiazide, Chlorothiazide, Chlortalidone [Chlorthalidone], Cilazapril with hydrochlorothiazide, Cyclopenthiazide, Enalapril maleate with hydrochlorothiazide, Indapamide, Lisinopril with hydrochlorothiazide, Losartan, Losartan potassium with	Antiplatelets Aspirin Clopidogrel Ticagrelor Dipyridamole Prasugrel Ticlopidine Hydrochloride Anticoagulants Warfarin sodium Dabigatran Phenindione Rivaroxaban	Pravastatin Simvastatin Atorvastatin Fluvastatin Ezetimibe with simvastatin Acipimox Bezafibrate Cholestyramine Clofibrate Colestipol hydrochloride Ezetimibe Ezetimibe with simvastatin Gemfibrozil Nicotinic acid	Heart failure Bumetanide Frusemide Metolazone Diabetes Insulin lispro Insulin neutral Insulin isophane Insulin zinc suspension Insulin aspart Insulin glargine Glucagon hydrochloride Metformin hydrochloride Rosiglitazone Tolbutamide Tolazamide Glipizide Gliclazide Glibenclamide Acarbose Pioglitazone

hydrochlorothiazide, Losartan with hydrochlorothiazide, Losartan with Hydrochlorothiazide, Methyclothiazide, Methyldopa with hydrochlorothiazide, Quinapril with hydrochlorothiazide, Triamterene with hydrochlorothiazide Amiloride hydrochloride, Amiloride hydrochloride with furosemide, Amiloride hydrochloride with hydrochlorothiazide, Clonidine, Clonidine hydrochloride, Clonidine Hydrochloride, Hydralazine hydrochloride, Methyldopa, Methyldopa with hydrochlorothiazide, Pindolol with clopamide, Triamterene with hydrochlorothiazide			

Appendix 4: : ICD-10-codes used to determine history of cardiomyopathy, cardiac valve disease and cadiac valve prosthesis or cardiac device (ICD or pacemaker)

Category	ICD-10 Clinical Code	
Cardiomyopathy	E1053	Type 1 diabetes mellitus with diabetic ischaemic cardiomyopathy
	E1153	Type 2 diabetes mellitus with diabetic ischaemic cardiomyopathy
	E1353	Other specified diabetes mellitus with diabetic ischaemic cardiomyopathy
	E1453	Unspecified diabetes mellitus with diabetic ischaemic cardiomyopathy
	I255	Ischaemic cardiomyopathy
	I420	Dilated cardiomyopathy
	I421	Obstructive hypertrophic cardiomyopathy
	I422	Other hypertrophic cardiomyopathy
	I423	Endomyocardial (eosinophilic) disease
	I424	Endocardial fibroelastosis
	I425	Other restrictive cardiomyopathy
	I426	Alcoholic cardiomyopathy
	I427	Cardiomyopathy due to drugs and other external agents
	I428	Other cardiomyopathies
	I429	Cardiomyopathy, unspecified
	I430	Cardiomyopathy in infectious and parasitic diseases classified elsewhere
	I431	Cardiomyopathy in metabolic diseases
	I432	Cardiomyopathy in nutritional diseases
	I438	Cardiomyopathy in other diseases classified elsewhere
	R570	Cardiogenic shock
Valve disease	3827001	Percutaneous balloon aortic valvuloplasty
	3827002	Percutaneous balloon mitral valvuloplasty
	3827003	Percutaneous balloon pulmonary valvuloplasty
	3845610	Open valvotomy of aortic valve
	3845611	Open valvotomy of tricuspid valve
	3845615	Other intrathoracic procedures on aortic valve without cardiopulmonary bypass
	3845616	Other intrathoracic procedures on mitral valve without cardiopulmonary bypass
	3845617	Other intrathoracic procedures on tricuspid valve without cardiopulmonary bypass
	3845618	Other intrathoracic procedures on pulmonary valve without cardiopulmonary bypass
	3847500	Mitral valve annuloplasty
	3847501	Tricuspid valve annuloplasty
	3847502	Aortic valve annuloplasty
	3847700	Mitral valve annuloplasty with ring insertion

	3847701	Tricuspid valve annuloplasty with ring insertion
	3847702	Aortic valve annuloplasty with ring insertion
	3848000	Repair of aortic valve, 1 leaflet
	3848001	Repair of mitral valve, 1 leaflet
	3848002	Repair of tricuspid valve, 1 leaflet
	3848100	Repair of aortic valve, >= 2 leaflets
	3848101	Repair of mitral valve, >= 2 leaflets
	3848102	Repair of tricuspid valve, >= 2 leaflets
	3848300	Decalcification of aortic valve leaflet
	3848500	Reconstruction of mitral valve annulus
	3848501	Decalcification of mitral valve
	3848700	Open valvotomy of mitral valve
	3848800	Replacement of aortic valve with mechanical prosthesis
	3848801	Replacement of aortic valve with bioprosthesis
	3848802	Replacement of mitral valve with mechanical prosthesis
	3848803	Replacement of mitral valve with bioprosthesis
	3848804	Replacement of tricuspid valve with mechanical prosthesis
	3848805	Replacement of tricuspid valve with bioprosthesis
	3848806	Replacement of pulmonary valve with mechanical prosthesis
	3848807	Replacement of pulmonary valve with bioprosthesis
	3848808	Percutaneous replacement of aortic valve with bioprosthesis
	3848809	Percutaneous replacement of mitral valve with bioprosthesis
	3848810	Percutaneous replacement of tricuspid valve with bioprosthesis
	3848811	Percutaneous replacement of pulmonary valve with bioprosthesis
	3848900	Replacement of aortic valve with homograft
	3848901	Replacement of aortic valve with unstented heterograft
	3848902	Replacement of mitral valve with homograft
	3848903	Replacement of tricuspid valve with homograft
	3848904	Replacement of pulmonary valve with homograft
	3848905	Replacement of pulmonary valve with unstented heterograft

	3849000	Reconstruction and reimplantation of subvalvular structures
	I050	Mitral stenosis
	I051	Rheumatic mitral insufficiency
	I052	Mitral stenosis with insufficiency
	I058	Other mitral valve diseases
	I059	Mitral valve disease, unspecified
	I060	Rheumatic aortic stenosis
	I061	Rheumatic aortic insufficiency
	I062	Rheumatic aortic stenosis with insufficiency
	I068	Other rheumatic aortic valve diseases
	I069	Rheumatic aortic valve disease, unspecified
	I070	Tricuspid stenosis
	I071	Tricuspid insufficiency
	I072	Tricuspid stenosis with insufficiency
	I078	Other tricuspid valve diseases
	I079	Tricuspid valve disease, unspecified
	I080	Disorders of both mitral and aortic valves
	I081	Disorders of both mitral and tricuspid valves
	I082	Disorders of both aortic and tricuspid valves
	I083	Combined disorders of mitral, aortic and tricuspid valves
	I088	Other multiple valve diseases
	I089	Multiple valve disease, unspecified
	I091	Rheumatic diseases of endocardium, valve unspecified
	T820	Mechanical complication of heart valve prosthesis
	T826	Infection and inflammatory reaction due to cardiac valve prosthesis
	Z952	Presence of prosthetic heart valve
	Z953	Presence of xenogenic heart valve
	Z954	Presence of other heart-valve replacement
cadiac valve prosthesis or cardiac device (ICD or pacemaker)	3827800	Insertion of permanent transvenous electrode into atrium
	3827801	Insertion of permanent transvenous electrode into ventricle
	3828100	Insertion of chamber pacemaker, not elsewhere classified
	3828101	Insertion of permanent single chamber pacemaker, VOO
	3828102	Insertion of permanent single chamber pacemaker, VVI
	3828103	Insertion of permanent single chamber pacemaker, VVT
	3828104	Insertion of permanent single chamber pacemaker, AOO
	3828105	Insertion of permanent single chamber pacemaker, AAI
	3828106	Insertion of permanent single chamber pacemaker, AAT
	3828107	Dependence on artificial heart
	3828108	Insertion of permanent dual chamber pacemaker, VDD

	3828 109	Insertion of permanent dual chamber pacemaker, DVI
	3828 110	Insertion of permanent dual chamber pacemaker, DDD
	3828 400	Insertion of permanent dual chamber transvenous electrodes
	3835 000	Insertion of permanent transvenous electrode into other heart chamber(s) for cardiac pacemaker
	3835 001	Replacement of permanent transvenous electrode of other heart chamber(s) for cardiac pacemaker
	3835 002	Removal of permanent transvenous electrode of other heart chamber(s) for cardiac pacemaker
	3835 003	Replacement of permanent transvenous electrode of other heart chamber(s) for cardiac defibrillator
	3835 004	Removal of permanent transvenous electrode of other heart chamber(s) for cardiac defibrillator
	3835 300	Insertion of cardiac pacemaker generator
	3835 301	Replacement of cardiac pacemaker generator
	3836 800	Insertion of permanent transvenous electrode into left ventricle for cardiac pacemaker
	3836 801	Replacement of permanent transvenous electrode of left ventricle for cardiac pacemaker
	3836 803	Replacement of permanent transvenous electrode of left ventricle for cardiac defibrillator
	3839 000	Insertion of patches for cardiac defibrillator
	3839 001	Insertion of permanent transvenous electrode into left ventricle for cardiac defibrillator
	3839 002	Insertion of permanent transvenous electrode into other heart chamber(s) for cardiac defibrillator
	3839 003	Replacement of patches for cardiac defibrillator
	3839 300	Insertion of cardiac defibrillator generator
	3839 300	Insertion of cardiac defibrillator generator
	3839 301	Replacement of cardiac defibrillator generator
	3845 623	Replacement of permanent epicardial electrode for cardiac pacemaker via subxyphoid approach
	3845 624	Replacement of permanent epicardial electrode for cardiac pacemaker via thoracotomy or sternotomy
	3845 630	Replacement of permanent epicardial electrode for cardiac defibrillator via subxyphoid approach
	3845 631	Replacement of permanent epicardial electrode for cardiac defibrillator via thoracotomy or sternotomy
	3847 000	Insertion of permanent epicardial electrode for cardiac pacemaker via thoracotomy or sternotomy
	3847 001	Insertion of permanent epicardial electrode for cardiac defibrillator via thoracotomy or sternotomy
	3847 300	Insertion of permanent epicardial electrode for cardiac pacemaker via subxyphoid approach
	3847 301	Insertion of permanent epicardial electrode for cardiac defibrillator via subxyphoid approach
	3852 100	Percutaneous insertion of patches for automatic defibrillator
	3852 101	Insertion of patches for automatic defibrillator

	38521102	Percutaneous insertion of defibrillation electrodes (leads) for automatic defibrillator
	38521102	Percutaneous insertion of leads for automatic defibrillator
	38521103	Insertion of defibrillation electrodes (leads) for automatic defibrillator
	38521103	Insertion of leads for automatic defibrillator
	38521104	Adjustment of electrodes (leads) for automatic defibrillator
	38521105	Replacement of patches for automatic defibrillator
	38521106	Replacement of electrodes (leads) for automatic defibrillator
	38521110	Percutaneous replacement of electrodes (leads) for automatic defibrillator
	38521400	Insertion of automatic defibrillator generator
	38521400	Insertion of automatic defibrillator generator
	38521402	Adjustment of automatic defibrillator generator
	38521403	Replacement of automatic defibrillator generator
	38651400	Insertion of permanent left ventricular electrode for cardiac pacemaker via thoracotomy or sternotomy
	38651401	Replacement of permanent left ventricular electrode for cardiac pacemaker via thoracotomy or sternotomy
	38651403	Insertion of permanent left ventricular electrode for cardiac defibrillator via thoracotomy or sternotomy
	38651404	Replacement of permanent left ventricular electrode for cardiac defibrillator via thoracotomy or sternotomy
	T820	Mechanical complication of heart valve prosthesis
	T821	Mechanical complication of cardiac electronic device
	T8255	Mechanical complication of artificial heart
	T8259	Mechanical complication of other specified cardiac and vascular devices and implants
	T826	Infection and inflammatory reaction due to cardiac valve prosthesis
	T8271	Infection and inflammatory reaction due to electronic cardiac device
	T8279	Infection and inflammatory reaction due to cardiac and vascular devices, implants and grafts, not elsewhere classified
	T8281	Haemorrhage and haematoma following insertion of cardiac and vascular prosthetic devices, implants and grafts
	T8282	Embolism and thrombosis following insertion of cardiac and vascular prosthetic devices, implants and grafts
	T8282	Embolism and thrombosis following insertion of cardiac and vascular prosthetic devices, implants and grafts
	T8283	Pain following insertion of cardiac and vascular prosthetic devices, implants and grafts
	T8284	Stenosis following insertion of cardiac and vascular prosthetic devices, implants and grafts
	T8284	Stenosis following insertion of cardiac and vascular prosthetic devices, implants and grafts
	T8285	Vascular dissection following insertion of cardiac and vascular prosthetic devices, implants and grafts
	T8285	Vascular dissection following insertion of cardiac and vascular prosthetic devices, implants and grafts

	T8286	Aneurysm following insertion of cardiac and vascular prosthetic devices, implants and grafts
	T8286	Aneurysm following insertion of cardiac and vascular prosthetic devices, implants and grafts
	T8289	Other specified complications of cardiac and vascular prosthetic devices, implants and grafts
	T8289	Other specified complications of cardiac and vascular prosthetic devices, implants and grafts
	T829	Unspecified complication of cardiac and vascular prosthetic device, implant and graft
	Z950	Presence of cardiac device
	Z952	Presence of prosthetic heart valve
	Z953	Presence of xenogenic heart valve
	Z954	Presence of other heart-valve replacement
	Z994	Dependence on artificial heart

Appendix 5: Baseline characteristics of women with non-CVD fatal event comparing to women with no event

		Fatal event		No event		p-value*
Participants (percentage of total cohort)		3,664 (2.1)		167,319 (97.9)		
Mean age, years (SD)		61.3 (8.5)		55.4 (8.8)		<0.001
Prioritised self-identified ethnicity, n (%)						<0.001
European	≥55 years	1,851 (63.6)		66,525 (68.1)		
	<55years	193 (25.6)		21,561 (31.0)		
Māori	≥55years	464 (15.9)		6,393 (6.5)		
	<55years	284 (37.6)		15,928 (22.9)		
Pacific	≥55years	380 (13.1)		6,815 (7.0)		
	<55years	217 (28.7)		16,906 (24.3)		
Chinese	≥55years	99 (3.4)		9,629 (9.9)		
	<55years	17 (2.3)		2,599 (3.7)		
Indian	≥55years	66 (2.3)		4,324 (4.4)		
	<55years	26 (3.4)		8,475 (12.2)		
Other Asian	≥55years	49 (1.7)		3,999 (4.1)		
	<55years	18 (2.4)		4,165 (6.0)		
NZDep quintile, n (%)						<0.001
1 (least deprived)		568 (15.5)		37,037 (22.1)		
2		575 (15.7)		33,384 (20.0)		
3		613 (16.7)		30,147 (18.0)		
4		795 (21.7)		30,690 (18.3)		
5 (most deprived)		1,113 (30.4)		36,061 (21.6)		
Smoking, n (%)						<0.001
Never smoker		2,184 (59.6)		122,782 (73.4)		
Ex-smoker		712 (19.4)		24,940 (14.9)		
Current smoker		768 (21.0)		19,597 (11.7)		
Mean SBP, mmHg (SD)		132.5 (16.7)		128.0 (16.0)		<0.001
Mean DBP, mmHg (SD)		79.0 (9.4)		78.3 (9.1)		<0.001
Mean TC/HDL (SD)		3.8 (1.3)		3.7 (1.1)		<0.001
eGFR, ml/min (IQR)		83.5 (70.0-94.7)		90.6 (79.0-100.0)		<0.001
Missing value of eGFR, n (%)		585 (16.0)		31,788 (19.0)		
BMI						<0.001
Underweight, BMI <18.5		86 (2.4)		1,651 (1.0)		
Normal weight, BMI 18.5-24.9		783 (21.4)		42,252 (25.3)		
Overweight, BMI 25.0-29.9		817 (22.3)		42,246 (25.3)		
Obese, BMI ≥30		1,268 (34.6)		52,625 (31.5)		
Missing value of BMI, n (%)		710 (19.4)		28,545 (17.1)		
Diabetes (%)						<0.001
No, n (%)	Hba1c level available, n (%)	2,921 (79.7)	1,456 (50.0)	146,748 (87.7)	89,175 (60.8)	
	Hba1c mmol/mol (SD) (where available)		40.0 (9.3)		38.7 (6.7)	
Yes, n (%)	Hba1c level available, n (%)	743 (20.3)	727 (97.8%)	20,571 (12.3)	20,208 (98.2%)	
	Hba1c mmol/mol (SD) (where available)		61.4 (20.5)		62.1 (20.2)	
Family history of premature CVD, n (%)		431 (11.8)		19,676 (11.8)		<0.001
History of atrial fibrillation, n (%)		85 (2.3)		1,476 (0.9)		<0.001

	Fatal event	No event	p-value*
Medication at index assessment, n (%)			
Antihypertensive medication	1,565 (42.7)	44,940 (26.9)	<0.001
Antithrombotic medication	719 (19.6)	16,466 (9.8)	<0.001
Lipid lowering medication	1,177 (27.7)	28,549 (17.2)	<0.001
Absolute 5-year CVD risk %, median (IQR)	4.9 (2.8-8.0)	2.1 (1.2-3.7)	<0.001

Note: BMI=body mass index; CVD=cardiovascular disease; DBP=diastolic blood pressure; eGFR=estimated glomerular filtration rate; Hba1c=haemoglobin A1C; HDL=high-density lipoprotein; IQR=interquartile range; N=number; NZDep=The New Zealand small-area index of relative socio-economic deprivation; SBP=systolic blood pressure; SD=standard deviation, TC=total cholesterol; *p for difference between women with non-CVD fatal event comparing to women with no event

Appendix 6: Baseline characteristics of men with non-CVD fatal event comparing to men with no event

		Fatal event		No event		p-value*
Participants (percentage of total cohort)		4,784 (2.2)		212,163 (97.8)		
Mean age, years (SD)		59.7 (9.6)		50.7 (9.9)		<0.001
Prioritised self-identified ethnicity, n(%)						<0.001
European	≥55 years	2,314 (68.4)		49,316 (68.4)		
	<55years	636 (45.4)		65,210 (46.6)		
Māori	≥55years	481 (14.2)		4,938 (6.9)		
	<55years	398 (28.4)		20,673 (14.8)		
Pacific	≥55years	361 (10.7)		5,457 (7.6)		
	<55years	262 (18.7)		24,385 (17.4)		
Chinese	≥55years	111 (3.3)		6,409 (8.9)		
	<55years	27 (1.9)		6,747 (4.8)		
Indian	≥55years	70 (2.1)		3,505 (4.9)		
	<55years	57 (4.1)		15,594 (11.1)		
Other Asian	≥55years	47 (1.4)		2,455 (3.4)		
	<55years	20 (1.4)		7,474 (5.3)		
NZDep quintile, n (%)						<0.001
1 (least deprived)		828 (17.3)		46,720 (22.0)		
2		778 (16.3)		42,585 (20.1)		
3		794 (16.6)		37,886 (17.9)		
4		974 (20.4)		39,067 (18.4)		
5 (most deprived)		1,410 (29.5)		45,905 (21.6)		
Smoking, n (%)						<0.001
Never smoker		2,368 (49.5)		139,150 (65.6)		
Ex-smoker		1,155 (24.1)		39,079 (18.4)		
Current smoker		1,261 (26.4)		33,934 (16.0)		
Mean SBP, mmHg (SD)		132.2 (15.9)		128.3 (14.6)		<0.001
Mean DBP, mmHg (SD)		80.0 (9.6)		80.0 (9.2)		<0.001
Mean TC/HDL (SD)		4.1 (1.3)		4.4 (1.2)		<0.001
eGFR, ml/min (IQR)		87.4 (74.5-96.7)		91.9 (81.4-101.7)		<0.001
Missing value of eGFR, n (%)		807 (16.9)		48,550 (22.9)		
BMI						<0.001
Underweight, BMI <18.5		59 (1.2)		670 (0.3)		
Normal weight, BMI 18.5-24.9		946 (20.0)		39,110 (18.4)		
Overweight, BMI 25.0-29.9		1,485 (31.0)		73,935 (34.9)		
Obese, BMI ≥30		1,397 (29.2)		63,798 (30.1)		
Missing value of BMI, n (%)		897 (18.8)		34,650 (16.3)		
Diabetes (%)						<0.001
No, n (%)	Hba1c level available, n (%)	3,817 (79.8)	1,866 (48.9)	191, 250 (90.1)	114,701 (60.0)	
	Hba1c mmol/mol (SD) (where available)		39.3 (8.3)		38.5 (7.4)	
Yes, n (%)	Hba1c level available, n (%)	967 (20.2)	948 (98.0)	20,913 (9.9)	20,545 (98.2)	

		Fatal event		No event		p-value*
	Hba1c mmol/mol (SD) (where available)		60.6 (20.8)		62.5 (20.4)	
Family history of premature CVD, n (%)		477 (10.0)		20,300 (9.6)		<0.001
History of atrial fibrillation, n (%)		165 (3.5)		3,076 (1.5)		<0.001
Medication at index assessment, n (%)						
Antihypertensive medication		1,669 (34.9)		42,255 (19.9)		<0.001
Antithrombotic medication		982 (20.5)		20,350 (9.6)		<0.001
Lipid lowering medication		1,469 (26.5)		35,267 (16.8)		<0.001
Absolute 5-year CVD risk %, median (IQR)		7.5 (4.2-11.7)		2.8 (1.6-5.3)		<0.001

Note: BMI=body mass index; CVD=cardiovascular disease; DBP=diastolic blood pressure; eGFR=estimated glomerular filtration rate; Hba1c=haemoglobin A1C; HDL=high-density lipoprotein; IQR=interquartile range; N=number; NZDep=The New Zealand small-area index of relative socio-economic deprivation; SBP=systolic blood pressure; SD=standard deviation, TC=total cholesterol; *p for difference between men with non-CVD fatal event comparing to men with no event